Dendritic cells and macrophages in the kidney: a spectrum of good and evil

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Abstract

Renal dendritic cells (DC) and macrophages (Mac) represent a constitutive, extensive and contiguous network of innate immune cells that provide sentinel and immune intelligence function. They induce and regulate inflammatory responses to freely-filtered antigenic material and protect the kidney from infection. Tissue–resident or infiltrating DC and Mac are key to the initiation and propagation of renal disease, as well as essential contributors to subsequent tissue regeneration regardless of its etiology and pathogenesis. Their identification, functional and phenotypic distinction, interplay and relationship with effector and regulatory adaptive immune cells is complex and incompletely understood. This review discusses both the common and distinct characteristics of these cells, as well as recent key advances in the field that have identified renal-specific functions of DC and Mac that enable these important, phagocytic, antigen-presenting, cells to mediate or mitigate intrinsic kidney disease. We also identify priority areas for further investigation and prospects for translational and therapeutic application of acquired knowledge.

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Introduction

The manifestations of kidney disease are protean and include acute kidney injury (AKI) due to ischemia-reperfusion or direct tubular cytotoxicity, autoimmune glomerulonephritis, and rejection of kidney transplants affecting glomerular, interstitial and vascular compartments. Increasing molecular evidence now demonstrates the pivotal role of non-parenchymal cells, predominantly dendritic cells (DC) and macrophages (Mac), in determining both renal tissue injury and subsequent reparative responses following diverse insults.

Advances in technology and the understanding of innate and adaptive immunopathological cellular responses have facilitated DC and Mac identification and assessment of their function in non-lymphoid solid organs such as the kidney. DC are long-established as vital, systemic sentinels capable of responding to endogenous and exogenous 'danger' signals that activate cells to initiate and propagate immune responses to inciting antigen (Ag) 1–3. Mac have also been defined as a distinct, but related population of Ag-presenting cells (albeit less potent than DC) whose primary function is tissue homeostasis and phagocytic clearance. Both cell types reside within the renal interstitium and possess the capacity to drive and regulate both protective and deleterious renal pathology.

In this review we examine the archetypal components of the non-parenchymal compartment in the kidney. We consider recent advances in understanding the discrete yet overlapping roles of both DC and Mac - a difficult task due to the significant degree of functional and phenotypic similarity between these mononuclear phagocyte populations (Figure 1). We also review how innovations such as identification of distinct lineage markers and gene expression profiles, use of transgenic mice, and implementation of methods for cell ablation have facilitated the discrimination of subsets of each cell type that function in tissue homeostasis and immune tolerance, acute and chronic inflammation, and alloimmunity. We note however that significant limitations remain with many of these models, particularly the capacity to accurately target DC/Mac to modulate disease outcome, as well as their relevance to human disorders.

What defines a DC or Mac?

There is considerable flexibility, heterogeneity and complexity in the monocyte-myeloid developmental lineage 4, and both DC and Mac arise from progenitor cells in the bone marrow (BM) under the influence of key growth factors: colony-stimulating factor 1 (csf-1), fms-like related tyrosine kinase 3 ligand (Flt3L), and granulocyte-macrophage colony stimulating factor (GM-CSF) (Figure 2). Furthermore, monocytes recruited from the circulation may become tissue Mac or inflammatory DC during disease processes 5, 6.

An important issue has been how best to define DC *versus* Mac (Figure 1) and this area remains controversial (see Box 1) 7–10. Currently there is no definitive cellular demarcation

and studies have tended to investigate either DC or Mac with segregation based on traditional views of identification. This research (predominantly in mouse models) has been based on the supposition that Mac or DC could be accurately identified by their expression level of the 'macrophage' markers F4/80 and CD11b or the 'DC marker' CD11c, but these markers are not exclusive [11]. BM-derived Mac may express CD11c *in vitro*, whilst a DC may express F4/80 and CD11b, suggesting that these markers do not identify an unique cell population. The incomplete restriction of such cell surface markers complicates the interpretation of experimental data based upon this method of cell identification. This should be borne in mind when interpreting studies involving conditional cell ablation, or using transgenic mice expressing the human diphtheria toxin receptor (DTR) under the control of the CD11b [12] or CD11c [13] promoter (*vide infra* and Table 2) since cells other than DC or Mac may be affected following DT administration. These caveats are important to acknowledge, as there is likely to be overlap of function between Mac and DC, depending upon biological context. It is also desirable to determine the expression levels of multiple cell surface markers if possible (e.g. F4/80, CD11b, CD11c, CD103, major histocompatibility complex [MHC] class II), as both the pattern and level of expression of these cell surface markers may be informative. The analysis of transcription factors typically expressed by DC or Mac has also been utilized to characterize cells [14]. Whilst DC and Mac may have overlapping functions such as Ag uptake and presentation, there are several core functions that may be considered separately.

DC and Mac – the basic immunological paradigm

Dendritic cells (DC)

DC represent a rare group of heterogeneous and potent BM-derived antigen presenting cells (APC) that play a critical role in immune surveillance and the instigation of immunity or tolerance. DC mediate a critical link between the innate and adaptive immunological armamentarium [1, 15], and control the generation of naïve and memory T cell responses [16]. DC arise from hematopoietic progenitor cells via developmental pathways that exhibit considerable plasticity [17]; their generation is governed predominantly by the hematopoietic growth factor Flt3L [18–20]. They are present in the peripheral circulation (<0.1% of total circulating leukocytes), but also reside in virtually all tissues (especially near portals of entry), and display broad maturational and functional diversity [1, 15]. They are highly proficient at both internalizing Ag and Ag processing [21]. Via a highly-orchestrated process, they subsequently present peptide fragments of processed foreign or self Ag bound to major histocompatibility complex (MHC) class I or II molecules to T cells bearing appropriate receptors [15]. Once activated in the periphery, DC exhibit enhanced migratory capacity and convey processed Ag to secondary lymphoid organs for T cell stimulation that requires both MHC (signal 1) and co-stimulatory molecules (signal 2) provided by the DC [22]. DC activation, maturation and migration are triggered by a wide array of cell surface-expressed receptors for Toll-like receptor (TLR) ligands, C-type lectins, cytokines and chemokines involved in inflammatory responses (well-reviewed in [3, 18, 23]).

Macrophages (Mac)

Mac also comprise a diverse group of innate immune regulatory cells that are particularly adept at phagocytosis of tissue debris and infectious material. They are rich in lysosomes, can also serve as APC, and play role in wound healing 24. Mac precursor populations arise from the BM with a similar lineage profile to DC, although their development, differentiation and proliferation are governed by csf-1 (also known as macrophage colony-stimulating factor [M-CSF]). Administration of csf-1 to mice post-natally increases kidney weight and Mac number 25. Mac arise during fetal life with a predominantly trophic role; developmentally their presence precedes the appearance of nephrons26, but they develop primary phagocytic function in adulthood27. Although the commonly accepted tenet is that Mac renewal within the interstitial compartment is derived from hematopoietic stem cells, recent evidence suggests contribution from embryonic progenitors28, 29 and *in situ* proliferation6, 30.

Several phenotypes that may be adopted by Mac led to the 'M1/M2 macrophage paradigm' in which M1 Mac (classically activated) are regarded as pro-inflammatory whilst M2 Mac (alternatively activated) are regarded as promoters of wound healing and fibrosis 31. These phenotypes have been defined by *in vitro* experiments and although undoubtedly simplistic, the M1/M2 concept emphasizes the fact that Mac, like DC, have inherent plasticity, so that the phenotype of individual cells and populations may change and evolve over time *in vivo* 32.

Renal DC and Mac in homeostasis

(i) Identification with the kidney

A range of mononuclear cells have been identified within the renal interstitum. $CD3^+$, $CD4^+$, $CD8^+$, $CD19^+$, and $CD3^-NK1.1^+$ lymphocytes have been isolated from unmanipulated rodent kidneys 33, as have regulatory $CD4^+CD25^+$34 and $\gamma\delta$ T cells 33, 35, in addition to DC and Mac. Although mouse DC were first described in the seminal papers of Steinman and Cohn 40 years ago36–38, their localization, and phenotypic and functional characterization was confined initially to DC within secondary lymphoid tissue. Although DC (and their multiple subtypes) have now been described within virtually all lymphoid and non-lymphoid tissues, formal identification of renal DC, particularly $CD11c^+$ DC, has been disputed. The renal DC population was thought initially to localize to the glomerular compartment and thus mediate the pathogenesis of glomerulonephritides. This assumption was supported by isolation of rodent glomerular cells phenotypically distinct from mesangial cells, that expressed MHC class II (Ia) and exhibited T cell allostimulatory capacity in primary mixed leukocyte cultures 39–42. Concurrent rodent and human studies confirmed the presence of MHC class II^+ cells within the cortical interstitium 43, 44. Electron microscopic examination of rodent peritubular interstitium enabled differentiation of fibroblasts from immune cells with features suggestive of DC (high expression of MHC class II) or Mac (abundant primary and secondary lysosomes)45. Immunohistochemical identification of $CD11c^+$ DC requires minimization of protein denaturation by avoiding high temperatures46, and has facilitated the detection and localization of DC proximate to peritubular capillaries47.

(ii) Phenotypic characterization

In mice, CD11c^{+} renal DC are heterogeneous, expressing MHC class II, CD11b and F4/80; although they exhibit allogeneic T cell stimulatory capacity, this is lower than that of splenic CD11c^{+} DC47. Extensive phenotypic characterization of conventional CD11c^{+} DC (cDC) has revealed an immature state (low CD80 and CD86, and negligible CD40 expression) and substantial phagocytic capacity, in addition to the absence of non-conventional plasmacytoid (p)DC markers (CD8α or B220),. CD11c^{+}MHC II^{+} renal DC segregate into two distinct subsets: CD103 (integrin αEβ7)[+] (CD11b^{lo}CX$_3$CR1^{-}F4/80^{-}SIRP-α^{-}) and CD11b^{+} (CD103^{-}CX3CR1^{+}F4/80^{+}SIRP-α^{+}), both of which divide in the steady-state48. CD103^{+} renal DC arise primarily from BM-derived precursor (pre)-cDC (see Figure 2), express higher inhibitor of DNA protein 2 (Id2) and interferon regulatory factor (IRF) 8, as well as Flt3. Both the Flt3 receptor and its ligand (Flt3L) are an absolute requirement for the development of this DC subset48. CD11b^{+} DC express csf-1 receptor (csf-1R) in keeping with a developmental bias towards this growth factor, but are also dependent upon Flt3L for complete reconstitution48.Mac, conventionally defined as CD11b^{+}, express greater levels of the csf-1R (CD115) whencompared to DC 49. The csf1R-enhanced green fluorescent protein transgenic-reporter mouse (the so-called 'MacGreen' mouse, *vide infra*) has been used to track Mac appearance post-natally, with cells present prior to nephrogenesis in close apposition to developing renal tubules and increasing with csf-1 treatment 26. Tissue-resident Mac derive from BM-resident monocyte precursors 50, which may also be characterized as CX3CR1^{+}CD117^{+}Lin^{-}; additional recruitment of Ly6C^{+} cells can occur under the influence of CCR2 (Figure 2)51. Tissue Mac derived from infiltrating monocytes may undergo differentiation into 2 broad categories depending on context: classically (M1) or alternatively-activated (M2) cells. M1 Mac may be induced by encountering danger-associated molecular pathogens (DAMPs) or pro-inflammatory cytokines, and produce IL-12 and IL-23 (as do DC) to promote CD4^{+} T helper (Th)cell polarization. . M2 Mac may develop from deactivated M1 Mac or arise *de novo*, and are immunoregulatory, and produce anti-inflammatory IL-10 as well as wingless-type MMTV integration site family member 7B (Wnt7B)52.

Studies in CX$_3$CR1[GFP/+] 53 and MacGreen 54 mice (Table 1) attest to the network of DC and Mac within the kidney, but despite improvements in renal DC characterization, absolute numbers following their isolation remain relatively low when compared to secondary lymphoid organs47. Systemic administration of Flt3L to mice55 and non-human primates56 has enabled expansion of both renal cDC and pDC *in vivo*. *Ex vivo,* freshly-isolated mobilized DC retain an immature phenotype and promote CD4^{+}CD25^{+} IL-10-producing regulatory T cells (Treg) 55. Low chemokine receptor (1, 2, 5 and 7) transcript levels by these DC reflect a failure to migrate *in vitro* in response to chemokines (CCL3, 5 and 20), although their migratory capacity to the lymphoid tissue-homing chemokines CCL19/20 can be augmented *ex vivo* by exposure to bacterial lipopolysaccharide (LPS)57.

While no candidate precursor for renal-resident DC has been formally identified, they are thought to be derived from common DC precursors that arise from BM progenitors and subsequent blood-borne pre-DC precursors58 (Figure 2). Ly6C^{-} 'patrolling' circulating monocytes may also contribute to renal resident DC, while Ly6C^{+} (Gr-1^{+}) cells infiltrate the

kidney under inflammatory conditions6, 59 in a manner requiring CX_3CR1 (the fractalkine receptor) 60.

The complexity of resident renal DC/Mac populations has been elegantly reinforced in recent work demonstrating multiple discrete subsets in the kidney, distinguished by cell surface markers, cytokine production, and transcription factor and chemokine receptor expression 14. The populations were initially defined according to the expression level of CD11b and CD11c. Subsets 1 and 4 exhibit a DC phenotype, and an ability to robustly stimulate $CD4^+$ T cell proliferation that includes induction of $Foxp3^+$ Treg. However, these cells also phagocytose latex beads, and express the Mac marker CD68 in conjunction with developmental and reparative growth factors such as insulin-like growth factor 1, platelet derived growth factor and Wnt7B . In contrast, subsets 2 and 3 display a Mac phenotype with phagocytic capability but an absent or limited capacity to induce T cell proliferation. These cells also express growth factors and produce IL-10 following LPS stimulation. Thus, the concept of overlapping DC/Mac characteristics should be borne in mind in experimental studies or transgenic mice that utilize a single cell marker such as CD11b, CD11c, CX3CR1 or csf-1R as these are all variably expressed by DC and Mac in the normal kidney. A further limitation when assessing DC/Mac populations, is that their characterization is based predominantly on whole kidney, rather than compartmentalized digests. Different renal microenvironments may well influence the presence of distinct DC/Mac subtypes leading to erroneous conclusions regarding cell localization: for example glomerular Mac fail to express F4/80 but may be identified by CD6861, 62.

(iii) Mouse models that enhance DC and Mac identification, imaging and function: reporter mice (Table 1)

Transgenic reporter mice, such as $CX_3CR1^{GFP/+}$ mice that map DC derived from CX_3CR1^+ monocytes discharged from the BM, have confirmed the homeostatic presence of renal DC throughout the entire interstitial scaffold, encasing glomeruli and present in low numbers within mesangial matrix53. The 'MacGreen' mouse54 allows visualization of Mac surrounding glomeruli and encasing renal tubular epithelial cells (RTEC) within the medulla (http://www.macrophages.com/macrophage-images).

(iv) Models of Mac and DC ablation (Table 2)

Various methods have been used to conditionally ablate Mac and/or DC *in vivo* with the aim of dissecting their function in disease (Table 2). Early work utilized the administration of liposomal clodronate that was toxic to phagocytic cells, particularly Mac63–67. The systemic administration of liposomal clodronate profoundly ablates Mac populations in the kidney, as well as liver and spleen, such that its effect may be secondary to intra-renal or extra-renal effects. Despite these caveats, the administration of liposomal clodronate has been used in multiple mouse and rat models of renal disease to selectively deplete DC and Mac (Table 4). Selective ablation has been attempted using transgenic mice expressing the human DTR under the control of the CD11b 12 or CD11c 13 promoter to deplete Mac or DC respectively following diphtheria toxin (DT) administration. Although it is inevitable that cells other than DC or Mac may also be deleted (Table 2), use of CD11b-DTR and CD11c-DTR mice has been highly informative.

Despite the apparent simplicity of cell depletion studies, there are multiple caveats to their interpretation. For example, what might be the possible explanations of an experiment in which depletion of CD11c^{+} cells reduced tissue injury? These would include i) the production of injurious factors by resident or infiltrating renal CD11c^{+} cells, ii) the production of protective factors by the residual surviving renal CD11c^{+} cells, other hematopoietic cells, or parenchymal cells (e.g. generated subsequent to interaction with the apoptotic corpses of ablated cells), iii) the promotion of systemic protective effects by renal or extra-renal CD11c^{+} cell depletion (e.g. skewing of immune responses), iv) the regeneration of CD11c^{+} cells following transient depletion might be protective, and any combination of these potential mechanisms.

Investigators have typically used a single cell ablation method, although the concurrent use of multiple methods can also be informative. Thus, administration of liposomal clodronate to CD11b-DTR mice was markedly protective against ischemia reperfusion injury (IRI), whilst administration of DT to CD11b-DTR mice had no effect on injury 68, 69. Intriguingly, the combined administration of both liposomal clodronate and DT to mice provides no protection i.e. the addition of DT removes the protective effect of the clodronate 69. These data suggest that the phenotype of the surviving residual cells in the kidney may be key to protection. These potential caveats and complexities should be borne in mind when cell ablation models are employed.

(v) Intrarenal DC and Mac function: cell recruitment, renal repair and fibrosis

Renal DC appear able to recruit other cells that perform immune functions. Thus, in a mouse model of *Escherischia coli* pyelonephritis, CD11c^{+} renal DC are the predominant producers of CXCL2 that recruits neutrophils to facilitate bacterial clearance70 (Figure 3), an effect that is impeded following conditional DC ablation (employing CD11c-DTR mice).

The progression of many experimental models of kidney injury (such as chronic allograft and diabetic nephropathy) can be limited by various maneuvers, but these do not typically lead to renal regeneration. Renal regeneration does occur, however, following moderate AKI induced by renal IRI and this has been used to explore the role of Mac in renal repair. Thus depletion of Mac using either liposomal clodronate 71 or DT treatment of CD11b-DTR mice during the reparative phase of AKI markedly retards restoration of tubular integrity and renal function. Recent work implicates Mac-derived Wnt7B and TLR4-induced IL-22 as key mediators of renal repair and tubular regeneration 52, 72.

Fibrosis is associated with progression of kidney disease to chronic renal impairment (well reviewed in 73, 74) . Mac may adopt a wound healing M2 phenotype during inflammation that promotes the production of extracellular matrix by myofibroblasts and scar formation (Figure 4). This is detrimental in the kidney, and may occur in conjunction with other pro-fibrotic processes such as epithelial cell cycle arrest75. Mac have been implicated in the development of renal fibrosis since administration of liposomal clodronate is protective in the rodent unilateral ureteric obstruction (UUO) model 76, 77. Interestingly, reduced fibrosis is evident in DT treated CD11b-DTR mice 6, 78, while DT treatment of CD11c-DTR mice does not reduce renal scarring 79, 80 despite the fact that renal DC exhibit increased maturation, activation and Ag-presenting capacity during UUO80. Studies involving the use

of BM chimeric-CD11b-DTR mice in which either renal resident DC/Mac or infiltrating BM-derived cells are depleted have demonstrated that resident renal non-parenchymal cells proliferate in UUO but do not actively contribute to fibrosis 6. The cells with a pro-fibrotic transcriptional profile were Ly6C^{lo} cells that had matured from kidney-infiltrating Ly6C^{high} monocytes 6. Also, persistent pro-inflammatory Mac activation promotes tubular atrophy and fibrosis following AKI 81. Collectively, these data suggest that Mac rather than DC may drive renal scarring but the mechanism is unclear. Although transforming growth factor beta (TGFβ) 1 is believed to be a key pro-fibrotic cytokine, mice with Mac-specific deletion of TGFβ1 exhibited comparable levels of fibrosis after AKI or UUO suggesting that Mac-derived TGFβ1 is not critical 82. Mac-derived mediators such as the lectin galectin 3 78 may be important, but further work is needed to clarify their identity and role.

(vi) Extrarenal DC function

Following activation, renal DC traffic to the draining renal lymph node where they present Ag. Several studies have shed light on the behavior of these DC when exposed to antigenic material. CD11c$^+$ renal DC preferentially and rapidly endocytose small (40kDa) molecules, compared to splenic DC that endocytose larger (500kDa) Ag 83. DC in the draining renal lymph node also endocytose low molecular weight Ag that has been transported by cell-independent mechanisms. CD8$^+$XCR1$^+$Batf3$^+$ (basic leucine zipper transcriptional factor ATF-like 3) renal lymph node-based DC are capable of Ag cross-presentation to subsequently delete cytotoxic T cells in a programmed death ligand 1 (PD-L1)-dependent manner84. This implies a necessary tolerogenic function for renal DC continually exposed to innocuous Ag. This view is further supported by the finding that proteasomal processing of albumin *in vitro* by BM-derived rat renal DC allows these cells to prime and subsequently activate CD8$^+$ T cells85. Similar observations have been made in rats subjected to five-sixth nephrectomy to induce focal segmental glomerulosclerosis that demonstrated interstitial inflammation, including infiltrating CD11c$^+$OX62$^+$ DC85. Infiltrates were reduced in animals treated with the proteasome inhibitor bortezomib. In the same study, DC isolated from draining renal lymph nodes activated syngeneic CD8$^+$ T cells in a manner that was time-dependent and reduced by bortezomib treatment.

Systemic administration of LPS to mice initiates DC efflux from the kidney to the draining renal lymph node over 24 to 48 hours86, 87. Renal subcapsular placement of ovalbumin (OVA) and subsequent LPS administration results in DO11.10 (OVA-specific) CD4$^+$ T cell division in the ipsilateral renal lymph node with Ag presentation mediated by CD11c$^+$ renal DC. A similar migratory response has been seen following IRI. This work is mechanistically relevant to *ex vivo* analysis of Flt3L-mobilized renal DC that upregulate CCR7 in response to LPS57, a necessary requirement for DC migration to draining lymph nodes via CCL19 and 21.

Renal DC and Mac in intrisinc renal disease models (Tables 3&4)

Multiple rodent models exist as mimics of clinical renal disease to provide mechanistic insights into glomerular and tubular pathophysiology (well reviewed in 88). We discuss a

number of standard immunological and cytotoxin-based examples of renal disease where DC and/or Mac have been investigated extensively.

Glomerulonephritides

Use of ovine (or rabbit or goat) antiserum produced following vaccination with mouse renal cortex and then injected into mice, generates rapid and progressive glomerular damage (nephrotoxic nephritis - NTN). This mimics the crescentic glomerulonephritis (GN) seen in human autoimmune disease[89]. The glomerular-based Ag-Ab complex that is generated is captured by both DC and Mac and presented subsequently to T cells. The cells presenting Ag within the kidney during the initial injury phase of NTN are typically CD11c^{+}CD11b^{+} with a maturing phenotype[90]. Renal DC also induce CD4^{+} T cell proliferation *ex vivo* and promote concurrent secretion of IFNγ and IL-10. Tubulointerstitial DC release IL 1β to promote NLRP3 inflammasome-caspase-1 pathway activation[91]. Ly6C^{-} renal DC produce most of the pro-inflammatory tumor necrosis factor-α and IL12-23p40[90].

Renal DC may also provide a protective role in NTN as their deletion (in CD11c-DTR mice) at days 4 or 10 after disease induction aggravates the extent of injury[92]. The mechanism of DC-mediated renal protection in NTN centers on IL-10 production and regulation of Th1 responses [93, 94]. Initial evidence suggested that this effect might be mediated via enhanced expression of inducible costimulator (ICOS)-L specifically on renal DC, that could promote IL-10 secretion following its ligation by T cells [95]. In contrast, DC depletion at day 7 reduces the presence of effector DC and T cells[90], implying a biphasic role for DC in this disease process. Mac ablation (using CD11b-DTR mice) attenuates glomerular disease, tubular injury and the presence of effector CD4^{+} T cells [96]. Other methods that block either Mac recruitment or activation factors, such as CCL2 are also protective in GN [97, 98].

Rat mesangioproliferative GN (anti-Thy 1.1 GN) is produced by injection of mouse monoclonal antibody to Thy1.1 and results in mesangial-based Mac infiltration[99]. Anti-glomerular basement membrane (GBM) disease also demonstrates ingress (or localization of adoptively transferred) monocyte-derived Mac that proliferate within glomeruli and correlate with histopathological severity[100, 101], a phenomenon that can be reversed by inhibiting csf-1[102] or treatment with CD80/86 monoclonal antibody[103].

In a mouse model of podocyte immunopathology in which Ag are expressed in glomerular podocytes (so-called NOH mice) [104], glomerular infiltrates demonstrate increased CD11c^{+}CD11b[int/hi] DC, and CD11c^{-}CD11b^{+} Mac, as well as pro-inflammatory CD11c^{+}Gr1^{+} DC or CD11c^{lo}GR1^{+} Mac. In this model, DC produce IL-12 and upregulate CD86 and CD40, consistent with their activation; in addition, the DC component, and consequently the periglomerular infiltrates are eliminated in DT-treated NOHxCD11c-DTR mice. Presentation of Ag by DC to CD4^{+} T cells is intrarenal only and facilitates CD8^{+} cytotoxic T lymphocyte accumulation.

Lupus Nephritis

Systemic lupus erythematosus (SLE) is a common autoimmune disease with a clinical predilection for catastrophic renal involvement. In animal models, the majority of studies have centered on the role of systemic DC in disease pathogenesis. However, the role of

kidney-resident DC and Mac in disease initiation and progression have been increasingly described (Table 3).

NZB/WF1 mice develop lupus nephritis spontaneously and histologically this is characterized by extensive mononuclear cell infiltration. The presence of CD11b^{+}F4/80^{hi}CD80^{+}CD86^{+} Mac has been shown to correlate with disease severity [105], and intrarenal CD11b^{+}CD11c^{+} cDC express B lymphocyte chemokine (BLC, CXCL13) with the ability to recruit autoAb-producing B cells [106]. MRL-Fas(lpr) mice demonstrate age-dependent lupus nephritis that correlates with renal expression of C1q (a subcomponent of complement activation via the classical pathway) that is generated locally by renal CD11c^{+} DC[107]. The pro-inflammatory cytokine IL-12, produced intrarenally by both DC and Mac, promotes the accumulation of IFNγ-secreting T cells to foster progression of nephritis. Not surprisingly, MRL-Fas(lpr)IL-12^{-/-} mice demonstrate reduced renal damage and lower mononuclear cell infiltrates[108]. In contrast, overexpression of CCL2 promotes monocyte recruitment, mitigated by blockade of the chemokine or its receptor (CCR2)[109, 110]. B6.TC mice also develop GN with concomitant autoAbs. DC from these mice have higher T cell allostimulatory capacity and block the suppressive function of CD4^{+}CD25^{+} Treg via overproduction of IL-6[111], in addition to facilitating B cell autoAb production and proliferation[112]. NZM2328 mice also display a proliferative, gender-dependent GN[113]. Renal histology is characterized by intraglomerular CD11c^{+} DC that co-localize with T cells[114], while F4/80^{+} Mac are confined to interstitial regions, suggesting that intrarenal DC mediate the presentation of (auto)Ag to promote disease progression.

Targeting Dc and Mac regulates experimental renal disease

(i) GN

Administration of cyclophosphamide and/or co-stimulation blockade (CTLA4-Ig or anti-CD154 mAb) to NZB/WF1 mice decreases CD11c^{+} renal DC infiltrates and induces lupus remission [115]. Moreover, amelioration of disease in MRL-Fas(lpr) mice has been demonstrated using a p38 mitogen-activated protein kinase (MAPK) inhibitor [116] that decreases renal CD11c^{+} DC, including those producing high-mobility group box 1 (HMGB-1) displaying a mature phenotype [117]. Creation of NZB mice lacking IRF8 (and thus lacking pDC) or mice carrying a mutation of the peptide-histone transporter solute carrier family 15, member 4 (SLC15[4], that retain pDC incapable of producing type I IFN) demonstrate amelioration of lupus pathology, implicating pDC in lupus pathogenesis [118]. In perinuclear anti-neutrophil cytoplasmic Ab (pANCA) positive SCG/Kj mice[119], a novel triazolopyrimidine derivative (NK026680) that inhibits DC function suppresses multiple disease manifestations and Ab development[120].

Manipulation of the humoral immune response may also mitigate disease in GN. Ligation of Fc receptors (particularly FcγRIIb) by immunoglobulin provides an inhibitory signal to prevent TLR-mediated DC maturation and attenuate lupus nephritis following adoptive transfer of immature DC[121]. MRL-lpr mice lacking FcγRIIb also display greater B cell activity and DC-derived IL-12[122]. Administration of C-reactive protein reverses renal manifestations of NTN in a Mac-dependent manner[123]. Immune complexes also suppress Mac inflammatory responses via FcγRIIb[124] which is protective in a GN model[125].

Binding of tissue-bound Ab or immune complexes may also activate Mac to produce pro-inflammatory mediators via activation of various signal transduction pathways including spleen tyrosine kinase (Syk). The Syk inhibitor fostamatinib markedly ameliorates NTN in rats and limits Mac activation following treatment with aggregated IgG126.

(ii) AKI

Both IRI and cisplatin induce tubular epithelial cell coagulative necrosis. $CD11b^{lo}F4/80^{hi}$ DC and $CD11b^{hi}F4/80^{lo}$ Mac (both differentiated from $Ly6C^{hi}$ infiltrating cells) can be identified early (3 hours) following IRI 60, peaking at 24 hours and become predominantly Mac in phenotype. Ablation of DC exacerbates cisplatin-induced AKI127, although DC-mediated protection has been disputed in models of IRI 68, 128. Mac ablation may provide renal protection in an IRI model 129–131, that is reversed by adoptive transfer of the mouse Mac cell line RAW 264.7 cells71, 130. Mac also display distinct phenotypes depending upon time post-injury, with M1 predominance initially (1-3 days following reperfusion) and M2 skewing during repair (with critical Wnt7b52 and csf-1132 production) and phenotype switching following adoptive transfer 133. The significance of each Mac subset is reflected in loss-of-function experiments demonstrating that depletion of M1 cells reduces injury, while reduction in M2 cells delays tissue restoration in IRI-induced AKI133, 134.

In a variation of the DTR models described above, mice selectively expressing the DTR gene in proximal tubular epithelial cells (where a human heparin-binding epidermal growth factor construct is linked to the promoter region of gamma glutamyl transferase 1 specific to proximal tubule cells) develop AKI in response to DT132. Administration of DT leads to renal infiltration with $CD11b^{+}F4/80^{+}CD11c^{+}CX_3CR1^{+}CD86^{+}$ DC/Mac. Prior administration of liposomal clodronate worsens renal injury, increases mortality and blunts the rapidity of renal repair, as does the use of DT in mice concomitantly expressing DTR in both $CD11c^{+}$ DC and proximal tubules, demonstrating the necessity of DC/Mac for tubular recovery.

Ablation of $F4/80^{+}CD11c^{+}$ DC/Mac 24 hours after renal IRI using liposomal clodronate aggravates injury and retards regeneration by promoting pro-inflammatory cytokines and dampening intrinsic IL-10 release by these cells134. In the same model, injury is partly alleviated by adoptive transfer of $CD11c^{+}$ DC. The protective effects of IL-10 generated by renal DC have been seen in other models of AKI, including cisplatin nephrotoxicity. Renal DC express higher IL-10 levels following cisplatin treatment (with concomitant increases in IL-10R1 expression). Conversely, IL-10KO mice display enhanced cisplatin-mediated injury, as do chimeric mice with DC that lack the capacity to produce IL-10135. This finding is also in keeping with increased expression of ICOS-L on renal DC in cisplatin-treated mice127.

$CD11c^{+}$ DC may also provide protection against AKI by modulating the effects of additional cell populations. Thus the protective role of Treg (both $CD4^{+}CD25^{+}FoxP3^{+}$ and $CD4^{+}CD25^{+}IL-10^{+}$)136 induced by $CD11c^{+}$ DC following renal IRI has been well-recognized 137–140. Moreover, infusion of mesenchymal stem cells abrogates renal IRI (reviewed in 141), via an effect that is partly mediated by $CD11c^{+}$ DC142. The immature phenotype of tissue-resident DC and intrarenal $FoxP3^{+}$ expression are lost in DT-treated

CD11c-DTR mice administered mesenchymal stem cells, and partially restored by the adoptive transfer of CD11c^{+} DC although not if they lack IL-10. There is increasing evidence that the cytokine milieu associated with sterile inflammation established in IRI is modulated by renal DC/Mac to drive pathologic and reparative processes. RTEC express csf-1 to drive Mac proliferation *in situ*132, 143. TLR-activated RTEC limit classical Mac activation *in vitro* with results of Ab inhibition experiments suggesting a role for IL-10144. Furthermore, a series of *in vitro* and *in vivo* experiments demonstrated that RTEC can induce non-programmed, quiescent Mac or programmed pro-inflammatory M1 Mac to adopt a M2 phenotype that limits acute renal inflammation and promotes repair133. F4/80^{+}CD11c^{+} renal DC/Mac numbers remain static, and F4/80^{-} DC/Mac with a mature phenotype increase in IRI kidneys. TNF-α, as well as IL-6 and CCL2 are produced in greater quantities by renal DC isolated from ischemic kidneys, and *in vivo* depletion of DC diminishes total TNF-α secretion within the renal CD45^{+} cell compartment 145.

(iii) Unilateral ureteric outlet obstruction (UUO)

UUO is a well-characterized model in which early inflammation is followed by renal fibrosis. CD11c^{+} DC exhibit phenotypic maturation and enhanced Ag presentation to and activation of T cells following UUO, with accompanying interstitial infiltration by CD11b^{+}Gr-1^{+} or F4/80^{+} DC (depending upon the cell surface marker used)79, 80, 146. DC depletion in CD11c-DTR mice at various times following induction of UUO does not alter subsequent development of renal fibrosis79, 80 although this feature is ameliorated by Mac depletion in CD11b-DTR mice6 or by administration of liposomal clodronate77. Additional data confirm decreased IFNγ and IL-17 in T cells following DC depletion146. In addition, 3 distinct populations of CD11b^{+}Ly6C[hi/int/lo] Mac have been identified that derive from BM monocytes or tissue-resident Mac 6. This is in keeping with data demonstrating that CCL2 or CCR2 blockade (and thus recruitment of inflammatory-type monocytes/Mac) impedes Mac accumulation147, and that attenuation of Mac matrix metalloproteinase 9 production decreases fibrosis148.

Cell surface receptors that play a role in mediating AKI are often expressed concomitantly on renal parenchymal and interstitial cells. Single Ig IL-1-related receptor (SIGIRR), also known as Toll-IL-1 receptor 8 (TIR8), modulates TLR signaling responses, particularly APC function in response to LPS challenge and ischemic renal damage149, 150. Thus, SIGIRR-deficient mice display susceptibility to tissue damage, including renal IRI, with increased production of IL-6, CXCL2 and CCL2. This response is abrogated in WT mice transplanted with SIGIRR^{-/-} BM and subjected to renal IRI, as well as in SIGIRR^{-/-} mice given liposomal clodronate149. Transplantation of SIGIRR^{-/-} renal allografts in a fully–MHC-mismatched mouse model has also been associated with expansion and maturation of CD11b^{+}CD11c^{+} resident DC/Mac that prime T cells and impede the development of CD4^{+}CD25^{+}FoxP3^{+} Treg 151. Renal IRI-mediated induction of IRF 4 is localized to CD45^{+}CD11c^{+} DC/Mac, whereas IRF4^{-/-} mice have increased renal damage that is abrogated by liposomal clodronate152.

Transplantation

The involvement of DC and Mac in renal transplantation has been studied 153, but there is relatively little information concerning the effects of standard immunosuppressive agents on renal DC or Mac number and function. Both donor Mac and DC are transferred within the allograft at the time of transplantation, and then host DC/Mac are recruited into the transplant154, 155. Mac proliferate intensely within kidney allografts in the absence of immunosuppression, and this is promoted by csf-1 156. Early animal studies revealed the lack of MHC class II induction in kidney allografts when recipients received cyclosporine compared to untreated transplants157. Cyclosporine also increases DC number and maturation status in rats158, 159. Warm ischemia alone leads to loss of the CD11c+CD11b+CD103- DC subset, whereas cold ischemia results in additional loss of the CD103+ subset from syngeneic grafts and their replacement by host CD11b+CD11c+CD103+TNFα+ DC160.

The ability of DC to subvert the alloimmune response following transplantation has been documented extensively in the literature (well reviewed in 18). Given their typical immature phenotype 55 renal DC represent an ideal potential source of regulatory DC, however their use is limited by inherent difficulties in isolating adequate numbers of cells. Mobilization of mouse renal DC using Flt3L increases their absolute numbers for subsequent infusion prior to cardiac transplantation, prolonging allograft survival in the absence of immunosuppression55.

Mac are also significant contributors to both acute and chronic allograft injury in animal models. In loss-of-function studies, administration of liposomal clodronate mitigates functional and tissue injury in a rat renal transplant model without affecting lymphocyte numbers or activation status 161. Similarly, DT treatment of CD11b-DTR mice protects the renal allograft from acute injury and rejection 162. Use of a pharmacological antagonist of the csf-1/csf-1R pathway reduces tubulointerstitial injury163, Mac infiltration, acute cellular rejection and T cell activation164. Interestingly, the treatment had no effect on humoral rejection that occurred later in the model. Persistent Mac infiltration also characterizes the development of chronic allograft nephropathy in rodents 165, that is ameliorated by Mac-specific blockade166, 167.

Renal DC and Mac in human health and disease

DC and Mac in normal human kidneys have been studied less extensively than those in rodents. Currently, most studies demonstrate DC within renal parenchyma using immunohistochemistry and their putative function is based on animal models.Both cDC (BDCA1+[CD1c]+ DC-SIGN+[CD209]CD68+ and BDCA1+DC-SIGN-CD68-) and pDC (BDCA2+DC-SIGN-) have been demonstrated within the normal renal interstitium and are rarely present within glomeruli168.

Examination of human renal allograft biopsies during acute cellular rejection reveals an increased number of DC-specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN)+ DC, particularly intraglomerular cells168. BDCA-1+, BDCA-2 (CD303)+, and DC-LAMP (DC-lysosomal associated membrane protein 3, CD208)+ cells have also been

identified with in acutely rejecting renal allografts[168]. CCR1^{+}DC-SIGN^{+} DC are also evident following transplantation[169]. A recent publication demonstrated increased CD141^{hi}CLEC9A^{+} and CD1c^{+}CD1a^{-}DCSIGN^{-} mDC[170], as well as pDC in human allograft biopsies with histological evidence of fibrosis. The mDC phenotype suggested that they were derived from the peripheral circulation, as well as being the predominant source of TGFβ.

Mac (CD68^{+} cells) have also been identified in renal allografts with histological evidence of Ab-mediated[171, 172], acute cellular [173] and chronic rejection[174]. Impairment of estimated glomerular filtration rate correlated with Mac transcript sets in patients biopsied for cause[175], and histological changes of both interstitial fibrosis/tubular atrophy and inflammation were associated with a Mac signature in microarray analyses[176, 177]. It is unclear whether these data represent a subset of acute rejection or a reparative phase to injury. Glomerular[178, 179] or interstitial[180, 181] Mac infiltration is a poor prognostic sign and marker of unfavorable graft outcomes.

Mac infiltration has been shown to be associated with an adverse outcome in native kidney disease. CD68^{+} Mac infiltration is an independent risk factor for progression to end-stage renal disease in patients with membranous nephropathy[182]. Biopsies from patients with a diverse range of chronic kidney disease, demonstrate that Mac infiltration correlate with both chronic damage and serum creatinine[183], and these cells co-localize to areas of capillary rarefaction, implicating a role for Mac in microvasculature injury[184].

Early studies detected CD1b^{+} DC within active areas of interstitial inflammation and glomerular crescent formation[185]. Observations regarding DC-based infiltration have also been made in kidneys with IgA nephropathy[168]. In patients with lupus nephritis, increased numbers of BDCA-1, -3 (CD141; thymomodulin) and -4 (CD304; neuropilin-1) positive cells (putative cDC), infrequent DC-LAMP (CD208)[+] mature DC, and BDCA-2^{+}ChemR23 (chemokine receptor-like 1)[+] pDC are seen [186]. BDCA-1^{+} myeloid DC also express C1q, with concordant animal model data suggesting that intrinsic renal DC contribute to local C1q synthesis[107]. However, there may be compartmental separation of mononuclear cell subtypes, with CD68^{+}CD209^{+} tubulointerstitial cell accumulation but CD68^{+}CD209^{-} intraglomerular cells, as well as correlation between the number of DC and degree of renal injury[187]. Mature (DC-LAMP^{+}) DC are not present in healthy kidneys but are evident at low numbers in diseased tissue, including lupus nephritis [168, 188]. Cross-talk between T cells and DC is well-recognized in mouse models and there is evidence from human kidney samples that a similar interrelationship initiates an (in)appropriate immunological response. Biopsies of patients with anti-neutrophil cytoplasmic Ab (ANCA)-associated vasculitis demonstrate close proximity between CD3^{+} T cells and DC-SIGN^{+} DC[189]. Tertiary lymphoid structures that develop within the renal parenchyma following chronic Ag stimulation have also demonstrated clusters of follicular (CD21^{+}) DC expressing the B lymphocyte-specific chemokine BCA-1 (CXCL13) [190], and neolymphangiogenesis with admixed CD4^{+} and CD8^{+} T cells, CD20^{+} B cells, S-100^{+} cDC and pDC[191]. These observations suggest intrarenal Ag presentation by DC to T and B cells to promote a chronic, immune-mediated inflammatory response.

The presence of pDC within diseased kidney has been demonstrated in mouse models (*vide supra*), but their role in human disease has been disputed. The contribution of pDC to renal pathology has been most demonstrated consistently in lupus nephritis, where secretion of IL-18 by resident glomerular cells is a potent chemoattractant for IL-18R-expressing DC 192, 193. BDCA-2+ChemR23+ pDC are present in severe lupus nephritis. pDC are also evident in increased numbers following delayed graft function (compared to calcineurin inhibitor toxicity where there is a preponderance of myeloid DC)194.

Conclusions

Renal DC and Mac are phenotypically and functionally heterogeneous cells that regulate tissue responses to renal injury and disease. The considerable overlap between DC and Mac represents a continuum of phenotype, as well as plasticity of cells of the myeloid-monocytic lineage both *in vivo* and *in vitro*. Our knowledge of renal DC and Mac function lags behind that described for other organs. This limitation has been improved by advances in cell isolation, identification, *in vivo* propagation, and use of innovative genetically-modified mouse models. The central role of renal DC and Mac in homeostasis, as well as their capacity to modulate physiological function to drive immune or non-immune disorders, is increasingly recognized. These cells provide a reservoir for ongoing immunosurveillance within the renal tubulointerstitium extending to the draining lymph node, in addition to affording an immune privileged site within the glomerulus.

Extensive small animal work has provided an important basis for increased phenotypic and functional understanding, however a consensus regarding precise cell identification and extrapolation to human kidney disease is lacking providing avenues for future research (see Box 2). However, after several decades of research the question of whether renal DC and Mac constitute sufficiently specific targets for therapeutic intervention to potentially ameliorate kidney disease progression remains.

Acknowledgments

Biography

Angus W. Thomson is a Distinguished Professor of Surgery and Immunology at the Starzl Transplantation Institute, University of Pittsburgh School of Medicine. He trained in basic and applied immunology at the University of Birmingham, UK, received his PhD from the University of Aberdeen, UK and conducted postdoctoral research as an MRC Travelling Fellow at the Kolling Institute of Medical Research, University of Sydney, Australia. Dr. Thomson's principal research interests concern mechanisms underlying tolerance induction, the immunobiology and tolerogenicity of dendritic leukocytes, and cell therapy in transplantation. Dr. Thomson has received numerous NIH grants, and is Program Director of

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Jeremy Hughes graduated in medicine from the Universities of Cambridge and London and focused upon glomerular inflammation for his PhD studies as a MRC Clinical Training Fellow at the Royal Postgraduate Medical School in London. After a University lectureship in Nottingham, he undertook a 3 year Wellcome Advanced Fellowship in Seattle in Professor Richard Johnson's laboratory. He became a Wellcome Senior Fellow in Clinical Science at the University of Edinburgh in 2000 and is now Professor of Experimental Nephrology. He has broad research interests, including macrophage biology, hemeoxygenase-1, acute kidney injury and renal fibrosis.

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Natasha Rogers is currently a postdoctoral fellow at the Vascular Medicine and Starzl Transplant Institutes at the University of Pittsburgh, Pennsylvania, USA. She received her MD and PhD from the University of Adelaide, Australia. Following an internal medicine residency she specialized in Nephrology. She has a current research interest in transplantation, acute kidney injury and dendritic cell biology.

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Key points

- Dendritic cells and macrophages are distinct cell types but also demonstrate similarities in terms of ontogeny, phenotype and function

- Both cells are present within the renal interstitium and are critical to homeostatic regulation of the kidney environment

- Dendritic cells and macrophages increase in number following renal injury

- The manifestation of glomerular or tubular kidney disease, as well as the outcome in pre-clinical models is determined by the type of dendritic cell or macrophage involved

- A number of methods are available to eliminate dendritic cells or macrophages, but the effects are not renal-specific

Box 1

**DC *versus* Mac – why the confusion?**

- the markers are not exclusive

    – CD11c, F4/80, CD11b, MHC class II are all co-expressed

    – CD11c expression is induced with inflammation (in macrophages, neutrophils as well as DC)

- similar growth factors promote their development

    – mononuclear cells from progenitors requires M-CSF, GM-CSF and Flt3L

    – cell phenotype *in vitro* demonstrate plasticity depending on the growth factors used

    – CSF1R (a traditional macrophage marker) is expressed by all classical DC; CSF1 and CSF1R mutations cause significant DC population depletion

    – injection of CSF1 into mice causes expansion of CD11c$^+$ cells, including macrophages, conventional DC, and plasmacytoid DC

    – GM-CSF promotes DC development *in vitro*; GM-CSF produces alternative macrophage with 'mature DC-type' cytokine profile

- functions are similar

    – both are highly phagocytic

    – antigen presenting capacity is typically attributed to DC; macrophages can suppress T cell activation in an antigen-specific manner

Box 2

Renal DC and Mac – challenges for the future

- consensus regarding differences/similarities between DC and macrophages for appropriate identification and classification

  - glomerular *versus* tubulointerstitial

  - tissue-resident *versus* recruited

  - immunogenic *versus* tolerogenic

  - fibrotic *versus* reparative

- correlation of terminology between murine and human cells

- exploration of RTEC-DC-macrophage crosstalk

- expansion of understanding of DC/macrophages in non-immunological and chronic disease processes such as diabetic kidney disease

- development of models with kidney-specific DC/macrophage ablation

- emphasis on translational work and applicability of findings to clinical disease
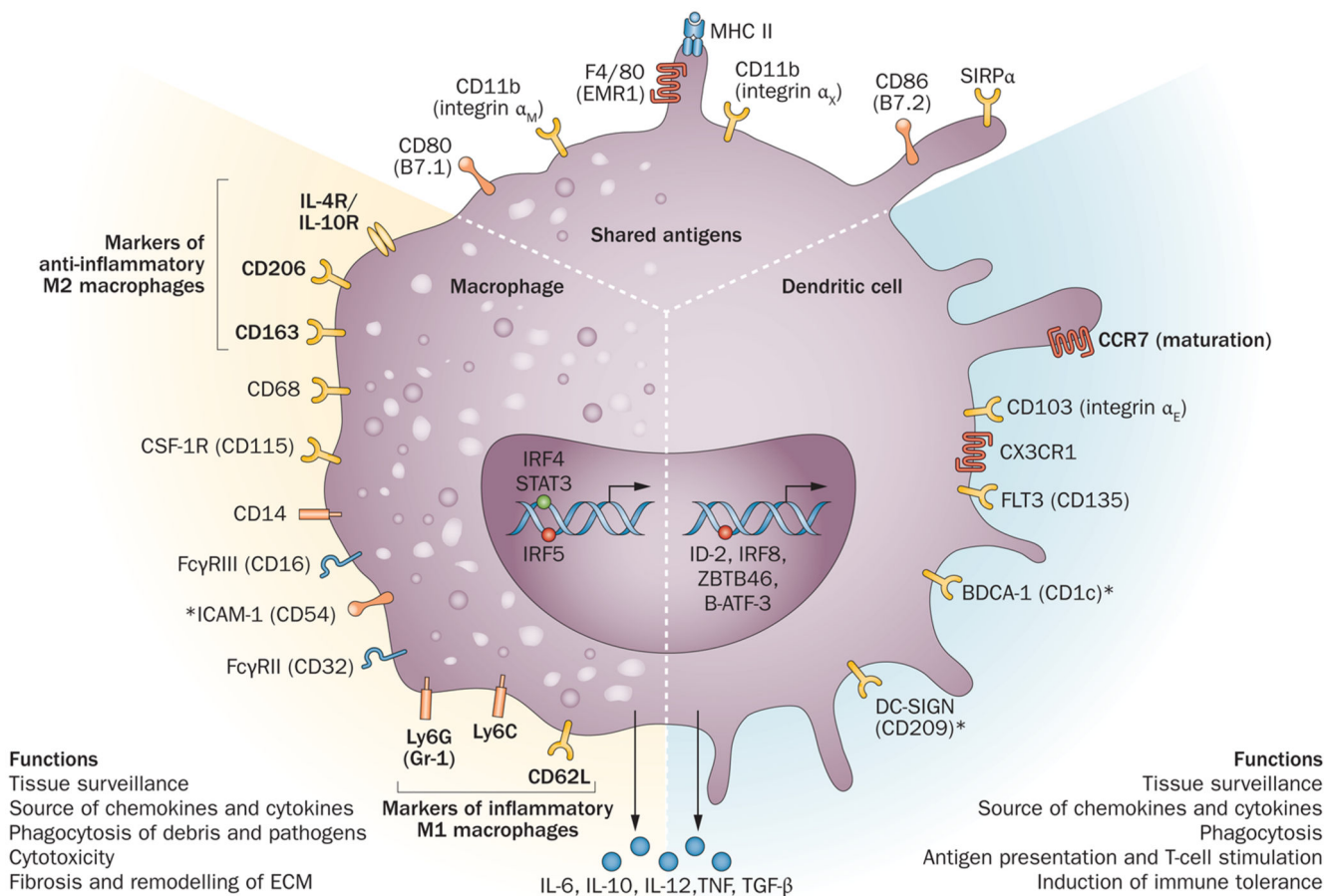
Figure 1. The heterogeneous but overlapping phenotype and function of renal DC and Mac
DC are traditionally described as mediators of immune surveillance and antigen presentation and the primary determinants of antigenic fate through initiation of immune effector cell function or the development of tolerance. Mac also function as innate immune cells predominantly through phagocytosis, and production of toxic metabolites. However, the classical paradigm of DC versus Mac is increasingly indistinct within the kidney, as these cells exhibit overlapping surface markers, functional capabilities, and ontogenic pathways. Abbreviations: AT3 – antithrombin 3; Batf3 – basic leucine zipper transcription factor ATF-like 3; csf – colony stimulating factor; DC-SIGN – dendritic cell-specific ICAM-3-grabbing non-integrin; flt3 – fms-like tyrosine kinase 3; ICAM – intercellular adhesion molecule; Id2 – inhibitor of DNA binding 2; IRF – interferon regulatory factor; SIRPα – signal regulatory protein alpha; STAT – signal transducer and activator of transcription; Zbtbf46 – zinc finger and BTB domain containing 46
* denotes human markers only
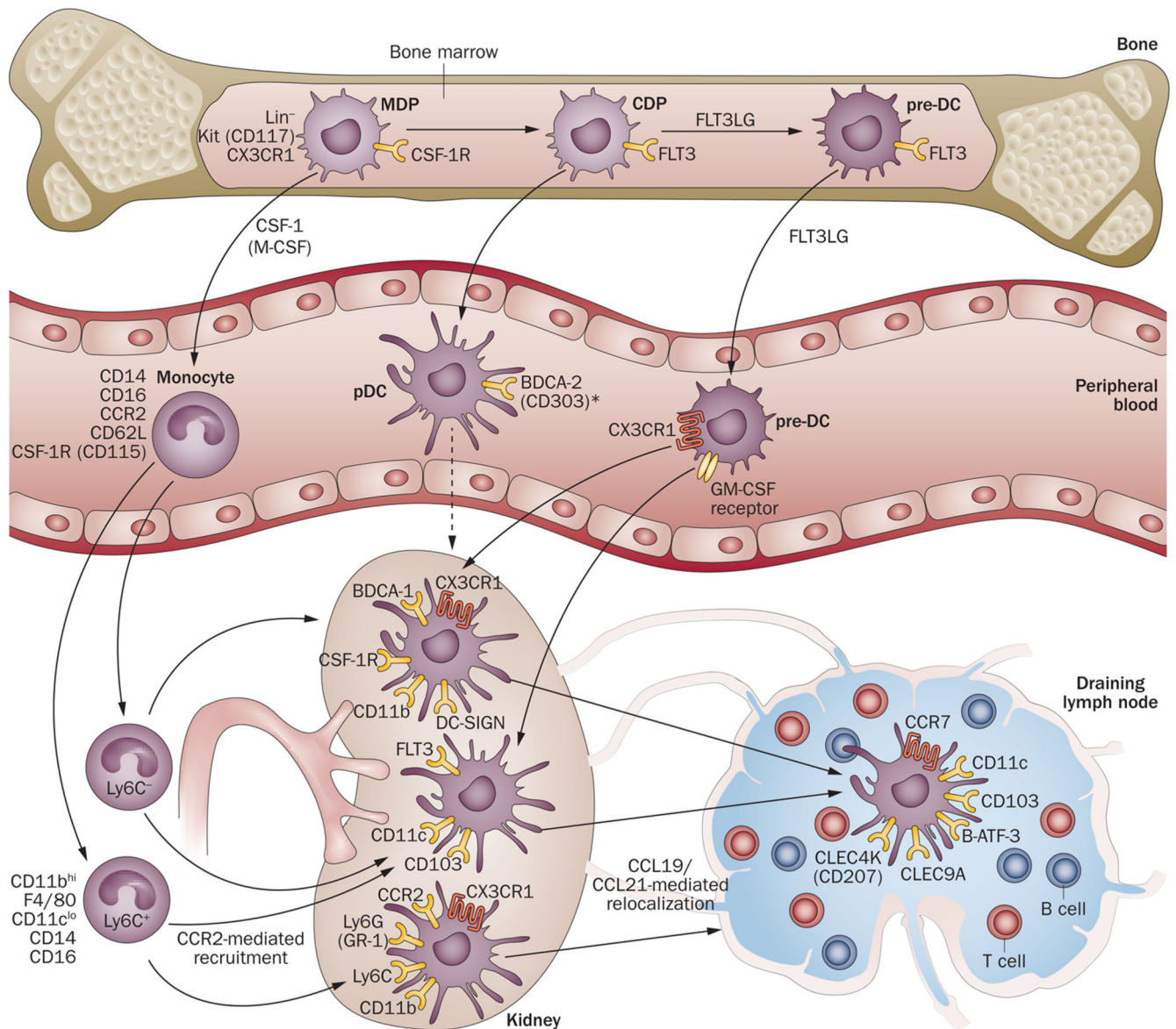
Figure 2. Ontogeny of renal-resident DC and Mac

Bone marrow-resident monocyte-dendritic cell precursors (MDP) release monocytes to the peripheral circulation under homeostatic and inflammatory conditions. Cells also develop into common and pre-DC precursors (CDP and pre-DC) that migrate from blood to the renal interstitial compartment, with regular turnover. Pre-DC under the influence of different growth factors, become distinct, tissue-based subsets (broadly characterized as CX3CR1^{+} or CD103^{+}) capable of exodus to the draining lymph node for antigen presentation to T cells. Pre-DC also give rise to plasmacytoid DC (pDC), although their presence in murine kidney is disputed.
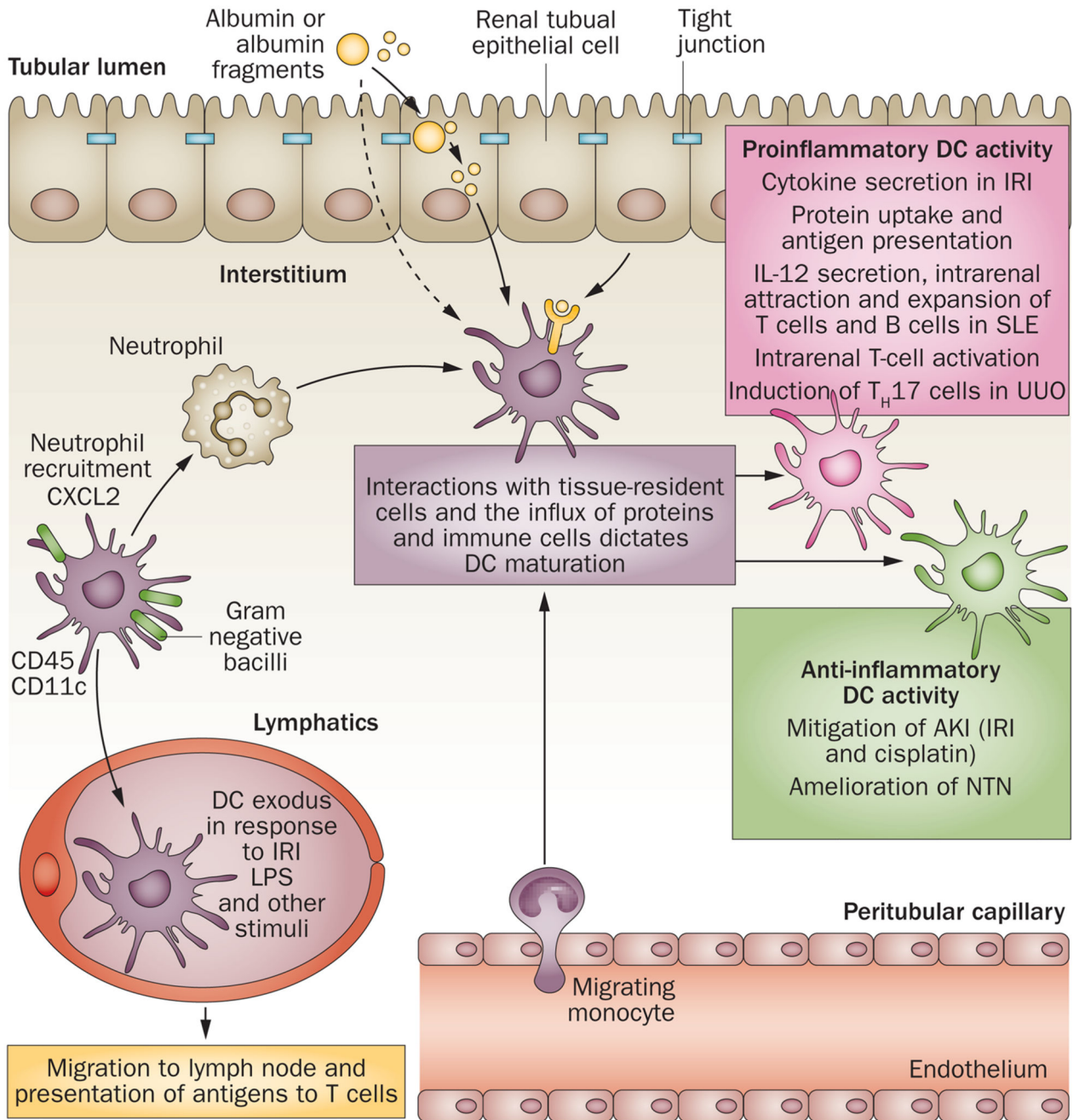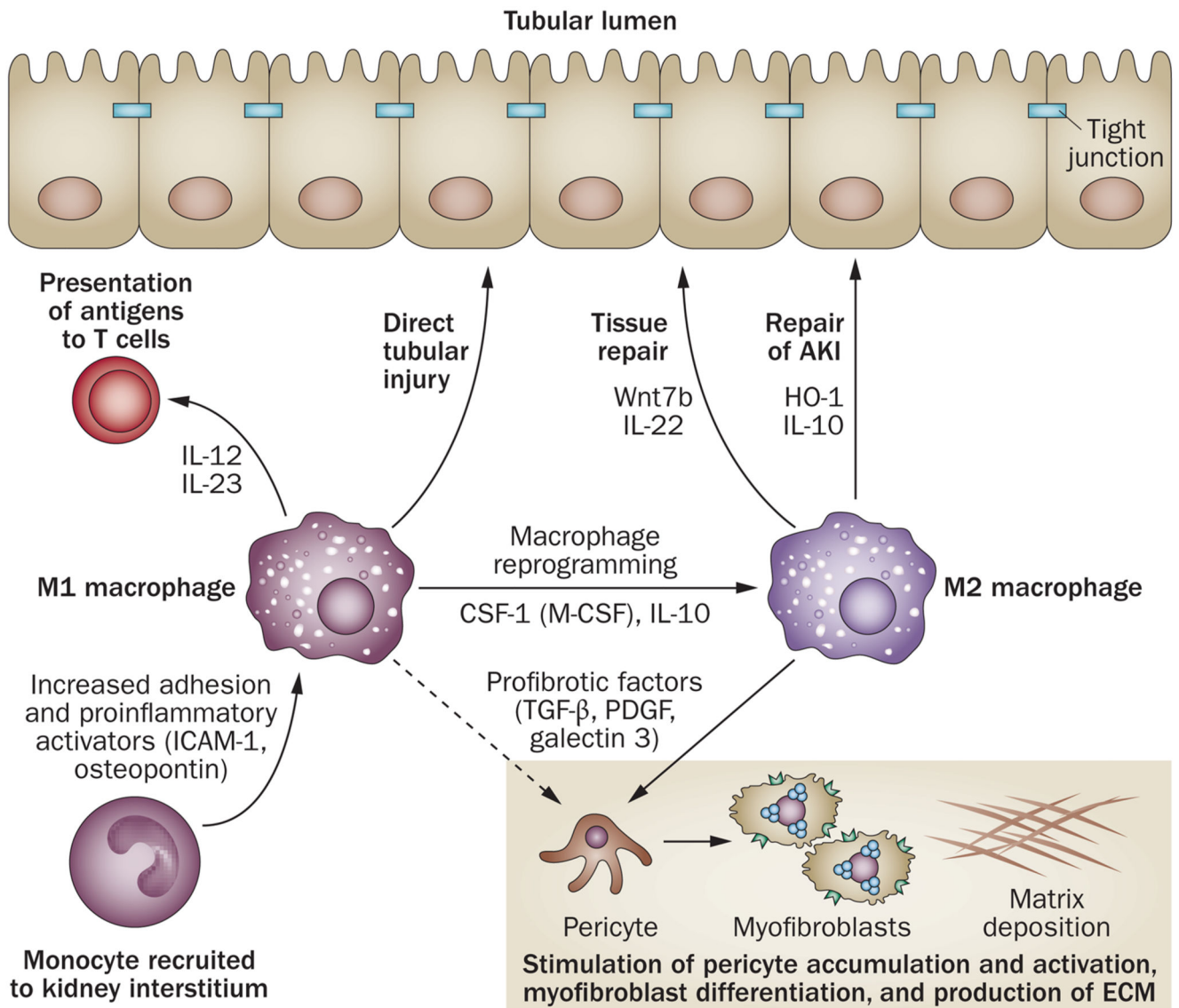
Figure 3. Renal DC function in health and disease
DC provide homeostatic functions including tolerance to peripheral antigens typically cleared by the glomerulus, and anti-infectious immunosurveillance. Interaction with bacteria promotes generation of chemokines to attract effector cells, such as neutrophils. DC responsiveness and maturation state may be regulated by ongoing interaction with tubular epithelial cells. They also operate to exacerbate or mitigate a wide range of parenchymal disease and this role may be determined by either tissue-resident or influxing cells.

Abbreviations: AKI – acute kidney injury; IRI – ischemia reperfusion injury; NTN – nephrotoxic nephritis; SLE – systemic lupus erythematosus; UUO – unilateral ureteral obstruction

Tubular lumen

Tight junction

Presentation of antigens to T cells

Direct tubular injury

Tissue repair
Wnt7b
IL-22

Repair of AKI
HO-1
IL-10

IL-12
IL-23

M1 macrophage

Macrophage reprogramming
CSF-1 (M-CSF), IL-10

M2 macrophage

Increased adhesion and proinflammatory activators (ICAM-1, osteopontin)

Profibrotic factors (TGF-β, PDGF, galectin 3)

Monocyte recruited to kidney interstitium

Pericyte   Myofibroblasts   Matrix deposition

Stimulation of pericyte accumulation and activation, myofibroblast differentiation, and production of ECM

Figure 4. Mac in renal disease

Tissue-resident Mac or infiltrating pro-inflammatory monocytes may become classically-activated (M1) to produce IL-12 and IL-23 and engage T cells for antigen presentation and activation or induce pro-fibrotic parenchymal change. M1 Mac may be reprogrammed to become alternatively-activated (M2) Mac by anti-inflammatory cytokines or apoptotic cell ingestion. M2 Mac may facilitate restoration of tubular cell integrity following injury . Mac may also express anti-inflammatory mediators such as HO-1 or IL-10 that act to limit tissue injury and promote resolution of inflammation, but may also drive pericyte and myofibroblast activation.

Abbreviations: AKI – acute kidney injury; HO-1 – heme oxygenase-1; ICAM-1 – intercellular adhesion molecule-1; M-CSF – macrophage colony-stimulating factor (also

known as csf-1); OPN – osteopontin; PDGF – platelet-derived growth factor; Wnt7b – wingless-related MMTV integration site 7B.

Table 1

DC and Mac reporter mice

Mouse model	Model basis	Utility	Cells identified	Disadvantages
CX$_3$CR1$^{GFP/+}$ 195	Coding exon on one allele of CX$_3$CR1 replaced by open reading frame for enhanced green fluorescent protein (eGFP)	Fate mapping of CX$_3$CR1 DC that differentiate from BM-derived monocytes of the same lineage	CD11b$^+$MHCII$^+$ CX$_3$CR1$^+$CD11c$^{+/-}$F4/80$^{+/-}$CD103$^-$ ie CD11b$^+$ type Mac (approximately 90% of total renal DC/Mac population)	Does not identify the remaining CD11b$^-$MHCII$^+$CX$_3$CR1$^-$CD11c$^+$F4/80$^-$CD103$^+$ cell population (estimated 5% of renal-resident DC)
MacGreen49, 54	EGFP gene driven by c-fms promoter (which encodes colony stimulating factor-1 receptor [CSF-1R]) combined with the first intron54	Identification of Mac	BM: 50% eGFP$^+$ cells are also F4/80$^+$ and CSF+1R$^+$ Peripheral blood: all eGFP$^+$ cells express F4/80 and CD11b Kidney: peri-epithelial Mac-like cells correlate with F4/80 expression, predominantly medullary location61	Does not distinguish cell subset

Table 2

Rodent models of DC and Mac ablation

Model	Mechanism	Utility	Specific Disadvantages
CD11c-DTR mouse196	Simian diphtheria toxin receptor-enhanced green fluorescent protein (DTR-eGFP) fusion gene inserted after the CD11c promoter;	Short-term (48h) ablation of 85-90% conventional DC *in vivo*, with preservation of plasmacytoid compartment 197, to a lesser extent cytotoxic T lymphocytes196 and NK cells 198 are affected. B cells and Mac unaffected	Depletes all CD11c$^+$ DC systemically, including F4/80$^+$ cells79 Late (>72h) neutrophilia 199 Repeated systemic administration of DT is lethal
CD11b-DTR mouse 200	DTR-eGFP fusion gene inserted after the CD11b promoter	CD11b$^+$ cells predominantly affected; CD3$^+$ T cells, B cells and neutrophils not affected	Depletes (>90%) all CD11b$^+$ cells systemically at 24h (Gr1$^-$CCR2$^-$CX3CR1$^+$ and Gr1$^+$CCR2$^+$CX3CR1$^-$); counts still low at 48h69
Liposomal clodronate67	Liposomes phagocytosed by Mac, followed by intracellular clodronate accumulation, cell dies by apoptosis66	Depletes phagocytic cells; total Mac (Gr1$^+$ and Gr1$^-$) decreased by >75% after 24h; Gr1$^+$ cells rebound higher69; preserved CD11c$^+$ population	All cells with significant phagocytic capacity potentially affected Clodronate leakage from dead/dying cells may affect inflammatory reactions65

Table 3

Experimental models of murine glomerular disease with known DC- and Mac-related pathogeneses

Model	Mechanism	DC/Mac function
Nephrotoxic nephritis (NTN)89	Glomerular injury- induced by the injection of mouse/rat renal cortex into a heterologous species (eg sheep, rabbits), then the Abs introduced into rodents	Ag/Ab complexes endocytosed by MHC II+ DC and Ag presented to CD4+ T cells. Mac are the main effector cells201. Aggravation of damage after early depletion of CD11c+ DC92.
Glomerulonephritis – (NOH mice 104)	Podocyte injury - the promoter for podocyte-specific human nephrin fused to cDNA encoding the transmembrane domain of the transferrin receptor, ovalbumin (OVA), and hen egg lysozyme (HEL)	Injection of activated OT-II (OVA-specific) Th cells, intra-renal stimulation. Periglomerular infiltrate, Mac-like: CD11c+, CD86+, MHC II+, CD11bhi/int, Gr1+
Lupus models:		
BWF1 mice 202	F1 hybrid strain created from mating New Zealand black and white mice205, 206	Mononuclear cell infiltration in kidney. Attraction of autoreactive T and B cells to kidney and expansion in draining lymph node114. CD11b+CD11c+ intrarenal DC/Mac are the source of B lymphocyte chemokine106.
B6.TC mice203	Mice homozygous for the NZM2410 lupus susceptibility QTL (*Sle1*, *Sle2* and *Sle3*)	DC from these mice demonstrate higher CD40 expression 207 DC have higher T cell allostimulatory capacity111
NZM2328 mice 204	Derived by selective inbreeding of progeny of a cross between NZB and NZW mice	Intraglomerular CD11c+ DC, F4/80+ Mac are confined to interstitial regions

Table 4

Rodent models of renal injury and the effect of DC or Mac depletion

Mouse model	Phenotype	DC/Mac effect	CD11c-DTR	CD11b-DTR	LipClo
AKI:					
UUO	Model of renal fibrosis	CD11b+Gr-1+ or F4/80+ DC interstitial infiltrate	No change in fibrosis79, 80	Reduced fibrosis6	Reduced fibrosis 77
IRI	Coagulative necrosis of renal tubular epithelial cells	Neutrophilic, Mac and CD11c+ DC interstitial infiltrate	Exacerbated 68; protection 128	Exacerbated 68; no change69	Exacerbated 134; protection 68, 69, 71; decreased TNF production 145
Cisplatin	Renally-excreted drug, concentrated in cortex; predominant damage is to S3 segment of the proximal tubule; coagulative necrosis of RTEC	Not described	At time of cisplatin treatment,- exacerbated injury 127	Not studied	Not studied
Adriamycin	Glomerular capillary permeability, tubular atrophy via ROS	Adoptive transfer of LPS-treated pDC ameliorates disease208	Not studied	Not studied	Not studied
GN:					
Nephrotoxic nephritis (NTN)	Crescentic GN (see Table 3)	DC capture Ag; present Ag to T cells	At day+4 or day+10, aggravates renal injury 92; depletion at day+7 reduces injury 90	Decreased glomerular crescents and proteinuria; improved renal function96	Decreased proteinuria 213; prevention of protection by CRP treatment 123
GN (NOH mice)	Podocyte-based glomerular pathology (see Table 3)	CD11c+CD11b+Gr-1+ glomerular infiltrates	Decreased CD11c+CD11b+Gr-1+ glomerular infiltrates	Not studied	Not studied
Lupus NZB/W mice	Severe GN with polyI:C 209	CD11b+GR1+F4/80+ glomerular infiltrates210	Not studied	Not studied	Decreased accumulation of Mac and glomerular injury 209
MRL.Fas(lpr) mice	See Table 3	Mature CD11c+ DC within kidney 117; TLR9 expression on DC and Mac in affected glomeruli 211	Decreased disease severity; autoAb formation (CD11c-DTR mice) 212	Not studied	Not studied
Infection Pyelonephritis	E. coli-induced 70	DC production of CXCL2 recruits neutrophils 70	Decreased neutrophil recruitment	Not studied	Not studied

Abbreviations: AKI – acute kidney injury; BM, bone marrow; CRP – C-reactive protein; GN – glomerulonephritis; IRF – interferon regulatory factor; IRI – ischemia reperfusion injury; LipClo, liposomal clodronate; LPS – lipopolysaccharide; ROS – reactive oxygen species; SIGIRR – single immunoglobulin and toll-interleukin-1 receptor; UUO – unilateral ureteric obstruction