Dendritic Cells and Macrophages: Sentinels in the Kidney

Christina K. Weisheit,*† Daniel R. Engel,*‡ and Christian Kurts*

Abstract

The mononuclear phagocytes (dendritic cells and macrophages) are closely related immune cells with central roles in anti-infectious defense and maintenance of organ integrity. The canonical function of dendritic cells is the activation of T cells, whereas macrophages remove apoptotic cells and microbes by phagocytosis. In the kidney, these cell types form an intricate system of mononuclear phagocytes that surveys against injury and infection and contributes to organ homeostasis and tissue repair but may also promote progression of CKD. This review summarizes the general functions and classification of dendritic cells and macrophages in the immune system and recapitulates why overlapping definitions and historically separate research have created controversy about their tasks. Their roles in acute kidney disease, CKD, and renal transplantation are described, and therapeutic strategy to modify these cells for therapeutic purposes is discussed.

*Institute of Experimental Immunology, University Clinic, Rheinische Friedrich-Wilhelms University, Bonn, Germany and †Clinic for Anesthesiology and Intensive Care, University Clinic, Rheinische Friedrich-Wilhelms University, Bonn, Germany; and ‡Institute for Experimental Immunology and Imaging, University Duisburg-Essen and University Hospital Essen, Essen, Germany

Correspondence:
Dr. Christian Kurts, Institute for Experimental Immunology, Rheinische Friedrich-Wilhelms University, Bonn, Germany. Email: ckurts@web.de

Introduction: General Roles of Dendritic Cells and Macrophages

All nonlymphoid tissues, including the kidney, harbor an intricate network of tissue-resident mononuclear phagocytes, which include dendritic cells (DCs) and macrophages. Macrophages were originally described >150 years ago by Slavjanski and Metchnikoff, and DCs were described by Steinman in 1973. These cell types are ontogenically related, and both serve sentinel roles but possess distinct hallmark functions. Macrophages are professional phagocytic cells that maintain tissue homeostasis (for example, by removing apoptotic cells) (Figure 1). During infection, they combat microbes by phagocytosis and production of toxic metabolites. Furthermore, they alert other immune cells by secreting proinflammatory chemokines and cytokines (1).

The canonical function of DCs is the activation of T cells (2). To this end, they gather antigens in tissues and transport them to draining lymph nodes to present them to specific T cells (3) (Figure 1). Immunogenic T-cell activation requires the DCs to have sensed pathogen-associated molecular patterns (PAMPs) or danger-associated molecular patterns (DAMPs; for example, bacterial cell wall components, like LPS). Without sensing such patterns, DCs remain in an immature functional state and cause antigen-specific T cells to undergo apoptosis. This is one major form of so-called peripheral tolerance, which serves as a second checkpoint (after thymic tolerance) against T-cell responses against autoantigens that are usually devoid of PAMPs (4). By contrast, DCs that have matured after sensing PAMPs or DAMPS can induce vigorous proliferation of specific T-cell clones, which are released into the circulation to infiltrate infected tissues to combat the pathogens. In addition to DCs that migrate into lymph nodes, there are tissue-resident DCs that regulate infiltrating effector T cells by producing cytokines and chemokines (5,6).

As a rule of thumb, macrophages are innate immune effector cells, and DCs induce adaptive immunity. Their sentinel and regulatory functions overlap, and the functionally dominant cell type depends on their tissue of residence. In this review, we will summarize the phenotypical and functional characteristics of macrophages and DCs in the kidney and describe their role in acute renal injury and CKD.

Ontogeny and Subsets of DCs and Macrophages

Several DC classification system have been defined in mice and humans on the basis of the expression of subset markers and functional properties (Table 1). Many authorities distinguish CD11b-like myeloid DCs (mDCs), CD8-like mDCs, Langerhans cells (important only in the skin and not further considered here), plasmacytoid DCs (pDCs), and inflammatory DCs (7–9). mDCs and pDCs are derived from a distinct DC precursor in the bone marrow, whereas inflammatory DCs, like inflammatory macrophages, originate from monocytes (10). The CD11b-like mDCs preferentially activate $CD4^+$ T helper cells, the CD8-like mDCs are specialized at activating $CD8^+$ cytotoxic T cells, and pDCs induce direct antiviral immunity by secreting type I IFNs. Inflammatory DCs can perform all of these functions and serve as a rapid supply of additional DCs in situations of need, such as infections. For more information on these important functions of DCs in mice and humans, we refer to recent excellent reviews (6,9,11).

Macrophages have been classified in the last decades according to the M1/M2 or the classic/alternative
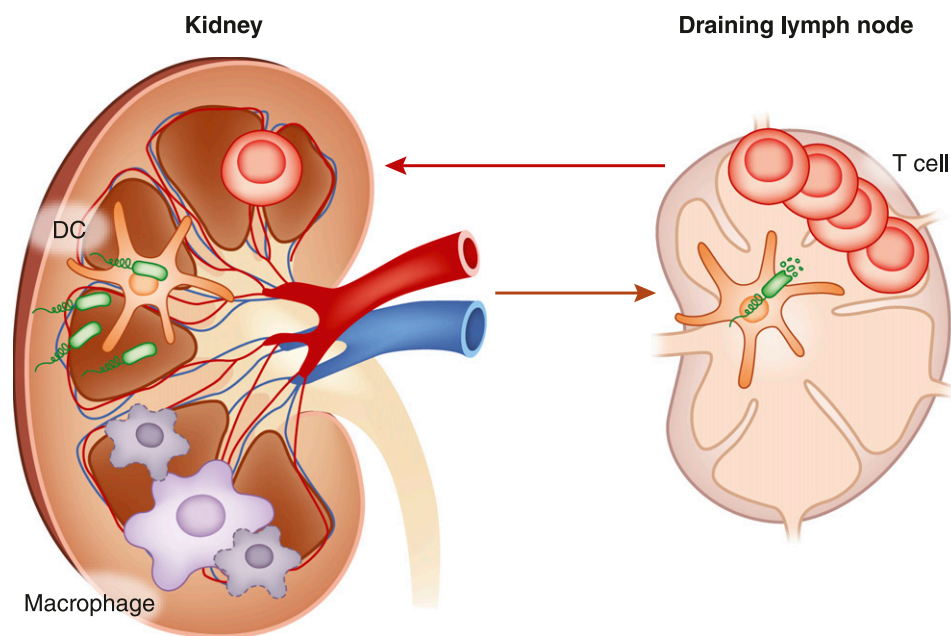
Figure 1. | Canonical functions of renal dendritic cells (DCs) and macrophages. Kidney DCs (orange) gather antigens (here represented in green as microbes) and transport them to draining lymph nodes to present them to specific T cells (red). Tissue-resident DCs can regulate activated T cells. Macrophages (violet) maintain tissue homeostasis, for example, by removing apoptotic cells. During infection, they may combat microbes by phagocytosis.

activation dichotomy, with the former performing proinflammatory antibacterial responses and the latter being involved in antiparasite immunity and tissue repair (12–14). However, these functions seem to represent merely two ends of a broad spectrum of macrophage polarization states (15). Another classification system uses the Ly6C marker to distinguish inflammatory and tissue-resident macrophages, which seem to perform distinct tasks in the anti-infectious defense (16,17). This difference is also evident in blood monocytes: in addition to the classic $Ly6C^+$ inflammatory monocytes that are dependent on the chemokine receptor CCR2, a distinct subset of $Ly6C^-$ monocytes expressing high levels of the chemokine receptor CX_3CR1 has been described (18). The latter seem to act as vascular sentinels that survey endothelial surfaces and may cause vasculitis and organ damage, which was explicitly shown in the kidney (19).

Recent work showed numerous other functional states of macrophages (20,21). This heterogeneity is further complicated by the discovery that certain tissue-resident macrophages, such as microglia and Langerhans cells, originate from not only the bone marrow but also, primitive precursors in the yolk sac and perhaps, the fetal liver (22,23). This finding has major implications for therapeutic strategies, because macrophages derived from primitive precursors seed organs before birth and multiply by local proliferation rather than recruitment from the circulation (24,25). Obviously, tissue-resident macrophages cannot be targeted by preventing their tissue recruitment in contrast to bone marrow–dependent macrophages. The classification of human tissue DCs and macrophages is less developed than that in mice because of technical limitations (21).

Discrimination between DCs and Macrophages

The realization that macrophages can also perform DC functions to a certain degree and *vice versa* has caused much uncertainty and debate about the exact demarcation between these two cell types. To understand this ambiguity, one has to remember that the fields of DC and macrophage research have historically developed more or less independent from each other. The marker molecules used to identify these cells considerably overlap; most notably, the murine DC marker CD11c used over three decades to distinguish DCs from macrophages is known to also be expressed by certain macrophages (for example, in the lung or the splenic marginal zone) (9,23). Likewise, the macrophage marker F4/80 is expressed by DCs in most nonlymphoid tissues, including the kidney (26) (Table 1). The systems commonly used to deplete DCs or macrophages for loss-of-function *in vivo* studies are often on the basis of these markers, and consequently, they are not specific either (27). Thus, many studies addressing either tissue macrophages or tissue DCs were unknowingly studying the same cells, often neglecting knowledge from the other discipline. In fact, the same mononuclear phagocyte may simultaneously fulfill the current criteria used by the DC community and those used by the macrophage community, because their definitions are not mutually exclusive.

Of course, semantic debates are of little importance to clinicians, let alone to patients. Therefore, many serious immunologists are currently discussing how to replace the numerous coexisting classification systems with a new system that is acceptable to both communities (28). Such a system will likely leave the current DC-macrophage dichotomy behind and encompass ontogenetic and functional properties. Before a consensus is reached, we will here adhere to

Table 1. General characteristics of dendritic cells and macrophages

Renal DC Subsets	Precursor Chemokine Receptors	General Functions	Key Markers Mouse	Key Markers Human	References
Myeloid/CD11b$^+$- like DCs	Common MDPs in the BM; CCR7, CCR2	Tissue surveillance; immune tolerance Ag transport to LNs, activation of T helper cells; recruitment of other immune cells to the kidney in GN and PN	CD11c^{high} F4/80$^+$ CX3CR1$^+$ CD11b$^+$	CD11c^{high} F4/80$^+$ BDCA-1$^+$	9,11
Crosspresenting DCs/ CD8α$^+$-like DCs	CDP XCR1$^+$	In renal LNs, CTL crosstolerance; very sparse in the kidney in lymph node T-cell activation; role within the kidney is unclear	CD11c^{high} CD11b$^-$ CLEC9A$^+$ XCR1$^+$ CD103$^+$	CD11c^{high} BDCA-3$^+$ CD14$^-$ CD1a$^+$	41,114
Plasma-cytoid DC	CDP	Possibly viral clearance through type I IFN; potential role in lupus nephritis	CD11c^{int} CD11b$^-$ CD8α$^-$ B220$^+$ Gr1$^+$	BDCA-2$^+$ CD11c$^-$	115
Monocyte-derived/ inflammatory DC	Monocyte-derived	Innate defenses against Tip-DCs proinflammatory cytokine production	CD11c$^+$ CD11b$^+$ F4/80$^+$ Ly6C$^+$	DC-SIGN/CD209a$^+$ requires additional study	9,10
Inflammatory macrophages/ Ly6C$^+$ macrophages	CCR2$^+$ MDP	Displays high phagocytic activity; cytokine release	F4/80$^+$ Ly6C$^+$ CD11c$^-$	CD14^{high} CD16$^-$	10
Ly6C$^-$ macrophages	CX3CR1$^+$ MDP Yolk sac derived	Sentinel function; initiation of inflammatory response Maintenance of tissue homeostasis; clearance of cell debris	F4/80$^+$ Ly6C$^-$ CD11c$^-$	CD14$^+$ CD16$^+$	22,24

DC, dendritic cell; MDP, monocyte–DC precursor; BM, bone marrow; Ag, antigen; LN, lymph node; PN, pyelonephritis; CDP, common–DC precursor; CTL, cytotoxic lymphocytes.

the current nomenclature, which classifies renal mononuclear phagocytes expressing CD11c as DCs and those lacking this marker as macrophages.

Pattern Sensors on DCs and Macrophages

DCs and macrophages express a great variety of receptors to sense microbial PAMPs. The best studied examples are the Toll-like receptors (TLRs), which detect cell wall components of gram-positive and -negative bacteria, flagellin, and bacterial and viral RNA and DNA. In addition, TLR2 and TLR4 also recognize self-components that are normally sequestered but released in situations of stress, sterile inflammation, or cellular damage. Such DAMPs signals generally include molecules like HMGB1, heat shock proteins, or fibronectin. DAMPs with more or less specificity to the kidney include uromodulin (Tamm–Horsfall protein), hyaluronan, and biglycan (29–31).

Table 2 lists these classes and additional classes of pattern-sensing receptors expressed by DCs and macrophages such as lectins, like the mannose receptor, dectins, or DC-SIGN, which recognize carbohydrate moieties, especially of microbial origin (32). Retinoic acid-inducible gene 1–like helicases are intracellular sensors that detect the presence of viral nucleic acids in the cytoplasm, whereas nucleotide-binding oligomerization domain receptors-like receptors recognize intracellular bacterial PAMPs (33). Much attention has recently been given to the NLRP3 inflammasome (Figure 2A), a large molecular complex that, in response to various types of crystals (*e.g.*, silica, asbestos, cholesterol, Alzheimer fibrils, and islet amyloid polypeptide), proteolytically activates in phagocytes IL-1, an inflammatory master regulator (34). Numerous other receptors deliver additional information (for example, cytokine receptors that inform about the activation state of neighboring cells, metabolic sensors that detect consumption of nutrients, or even neuronal synapses that provide a direct link to neural regulation). DCs and macrophages integrate all this information, respond with activation or maturation, and become proinflammatory. Numerous experimental studies have examined the role of these sensors in models of various diseases, including those affecting the kidney, and promising candidates for therapeutic intervention have been identified (35). However, most of these studies used mice ubiquitously deficient for these sensors, and therefore, it is unclear whether an observed beneficial affect can be attributed to DCs or macrophages.

DCs and Macrophages in the Kidney

The tubulointerstitium of healthy kidneys contains numerous CD11c$^+$ cells with extensive dendritic protrusions that can be classified by phenotypic and functional properties as tissue DCs of the CD11b type (Figure 3, Table 1) (26,36). Most of these DCs comply with some definitions of tissue macrophages (for example, in terms of F4/80 expression) (21,37). A recent detailed study showed that the murine kidney contains at least five discrete subpopulations of mononuclear phagocytes, which cannot be simply classified into the conventional entities, because they performed both traditional DC and macrophage functions to differing degrees (38). Cells with predominant DC functionality are more abundant in the cortical tubulointerstitium but mostly absent from the glomeruli (39,40). Only 5% of the tubulointerstitial DCs belong to the CD8-like subset that has exclusive DC functionality (41), but their role in the kidney is unknown. Cells with unambiguous macrophage phenotype can be found in small numbers within glomeruli (42) and in the subcapsular and periarterial connective tissues (43,44). Renal macrophages expressing very high levels of F4/80 originate mostly from the yolk sac (22) and are more abundant in the medulla (40). Renal mononuclear phagocytes are partially derived from common DC precursors and monocytes (45).

Most of these observations were made in mice, where numerous experimental tools are available. Extrapolation to the human system is not straightforward, because the subset markers differ substantially between species. This may be one reason why, until now, only a few studies have examined DC and macrophage subsets in human kidney biopsies (46–48). These revealed new insight into old

Receptor	MPh Versus DC	Disease	Functional Role	Reference
TLR3/7/9	MPh	Lupus model (MRL-Fas mice)	Harmful	116
TLR9	MPh	Lupus model (MRL-Fas mice)	Harmful	117
TLR4	DCs and MPh	Urinary tract infection	Protective	53
NLRP3, inflammasome	DC	Oxalat-induced AKI	Harmful	35,87
SIGIRR	DCs	IRI	Protective	62
A2AR	MPh	IRI	Protective	118
AT1R	MPh	Renal injury in obesity	Harmful	84
IL-17R	DCs and MPh	UUO	Harmful	85
TREM1	MPh	UUO	Harmful	86
uPAR	MPh	UUO	Anti-inflammatory but profibrotic	119

Table 2.   Selected pattern sensors relevant in kidney disease

TLR, Toll-like receptor; SIGIRR, single Ig IL-1–related receptor; uPar, urokinase receptor; NLRP3, NACHT, LRR, and PYD domains containing protein 3; A2AR, adenosine 2a receptor; AT1R, type I angiotensin receptor; TREM1, triggering receptor expressed on myeloid cells 1; MPh, macrophage; UUO, unilateral ureteral obstruction; IRI, ischemia reperfusion injury.
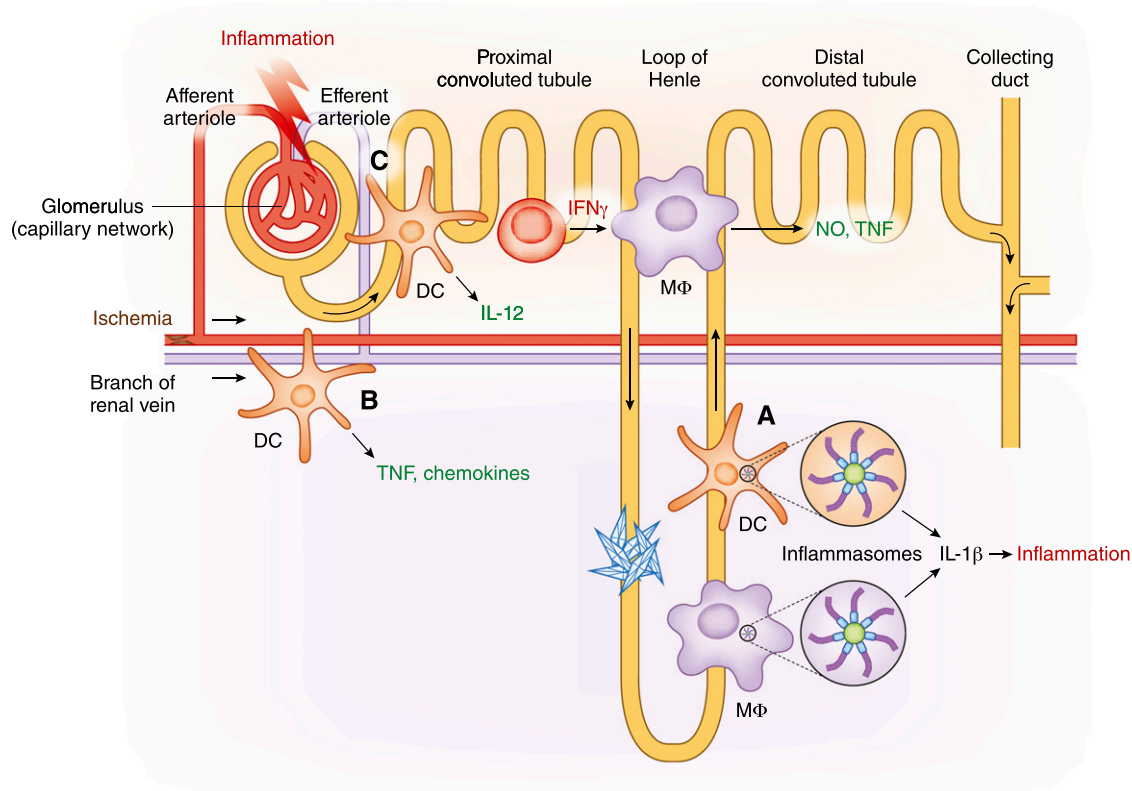
Figure 2. | **Role of renal DCs and macrophages in selected kidney diseases.** (A) Inflammasome activation in DCs and macrophages results from intratubular crystal formation, which is a consequence of the high osmolarity in the medulla that favors crystal formation. The inflammasome is an intracellular multimeric enzyme complex that contains adaptor proteins and caspase 1, which proteolytically activates IL-1β, resulting in inflammation. (B) Ischemia reperfusion injury activates DCs to produce TNF and chemokines that attract and stimulate injurious immune effector cells. (C) Glomerular inflammation activates periglomerular DCs in the renal cortex. They capture and present deposited or filtered antigens to CD4 T helper cells and stimulate these cells with IL-12. T cells secrete IFN-γ and cause macrophages to produce injurious mediators, like TNF or nitric oxide (NO). DCs, dendritic cells; MΦ, macrophage.

disease entities, such as shifts in the distribution and numbers of myeloid cells (identified in humans by the BDCA-1 marker) in lupus nephritis and necrotizing GN (47). There is great potential in this area to improve the histopathologic diagnosis of nephritis.

Homeostatic and Anti-Infectious Sentinel Functions
Maintaining Immune Tolerance against Renal Antigens
Kidney DCs constantly probe their environment using their dendrites, suggesting a sentinel role (26,36,46,49). Indeed, DCs in healthy kidneys continuously sample glomerular and tubular self-antigens and small molecular weight antigens that can constitutively pass the glomerular filter from the tubular lumen (50). It is unclear whether DCs do so by extending dendrites between epithelial cells into the tubular lumen as described for the intestine (51). In the absence of PAMPs, DCs express the suppressive molecule PDL-1 that induces apoptosis in T cells specific for such antigens (52). This function may serve to maintain immunologic tolerance against renal autoantigens or innocuous circulating small molecular weight antigens. However, this tolerance mechanism is undermined in diseases associated with proteinuria. When the glomerular filter becomes leaky, kidney DCs receive more proteins and in addition, high molecular weight antigens that stimulate potentially harmful T cells—another way that proteinuria can injure the kidney.

Defense against Urogenital Tract Infections
Renal DCs and macrophages use TLR4 to detect uropathogenic *Escherichia coli* (53,54), the most prevalent cause of kidney infections. DCs respond by producing chemokines that recruit neutrophilic granulocytes into the kidney to combat the bacteria by phagocytosis and production of toxic mediators (55) (Figure 4A). The DCs in the renal medulla are particularly potent at recruiting neutrophils (40), perhaps because they are the first to encounter the ascending bacteria and/or because of microenvironmental cues that cause them to specialize at anti-infectious functions. Notably, kidney macrophages contributed to neither the chemokine production nor the phagocytosis of uropathogenic *E. coli* (55). By contrast, another study reported that renal macrophages are critical for the defense against candida (56), which preferentially infect murine kidneys. The phenotype of the macrophages in that study (MHC II$^+$, F4/80$^+$, and CX$_3$CR1$^+$) resembles that of the DCs examined in the *E. coli* study, highlighting the current nomenclature
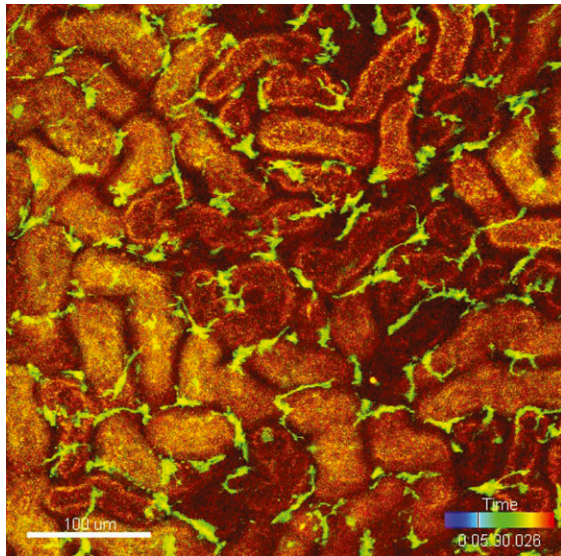
Figure 3. | **The renal mononuclear system.** Two-photon microscopy image of the renal mononuclear phagocyte system visualized by transgenic reporter mice in which cells, which include DCs, macrophages, and monocytes, harboring the receptor CX_3CR1 express green fluorescent protein. Reprinted from A. R. Kitching, with permission.

ambiguity resulting from overlapping definitions as described above.

By contrast, the defense against bacterial cystitis entirely depended on macrophages (more exactly on the interplay between two functionally distinct macrophage subsets that can be distinguished by expression of the Ly6C marker) (16) (Figure 4B). Bladder-resident $Ly6C^-$ sentinel macrophages performed a role comparable with the role of DCs in the kidney: they sensed the infection and produced chemokines that recruited neutrophils and $Ly6C^+$ monocytes. The latter did not directly combat bacteria but instead, performed an innate immune helper cell function. After sensing the infection, they produced the cytokine TNF as a helper signal that caused the sentinel macrophages to produce additional chemokines to guide neutrophils into the frontline of infection (the uroepithelium) to combat the bacteria. These findings showed that the immune system bases the decision of whether to induce antibacterial innate immunity on the agreement between several immune cells, probably to reduce the likelihood of false-positive decisions that would cause collateral damage—a principle well known from T- and B-cell responses of the adaptive immune system. These findings also help to explain why TNF is so important in antibacterial infection and why TNF-blocking therapies cause exacerbation of bacterial infections, including urogenital tract infections (57). It is unclear whether similar collaboration also occurs in the kidney during the defense against pyelonephritis. The finding that different myeloid cells act as sentinels in bladder and kidney highlights the close relationship between DCs and macrophages and the importance of microenvironmental factors that shape the local immune system. Exact knowledge of the mechanisms of antibacterial defense is important for designing superior therapies with minimal side effects.

Roles in Kidney Disease
AKI
Acute and chronic kidney inflammation is usually associated with the intrarenal accumulation of DCs and macrophages. Macrophages are widely considered important sources of proinflammatory cytokines and injurious mediators in various types of acute kidney diseases (58). In ischemia reperfusion injury (IRI), an important problem in kidney transplantation, kidney-resident DCs are the first to produce proinflammatory chemokines and cytokines like TNF (59), suggesting a proinflammatory role (Figure 2B). However, functional studies showed that kidney DCs prevented excess ischemic tissue damage (60,61), which has been linked to anti-inflammatory signaling mechanisms involving IFN regulatory factor 4 and immunosuppressive mediators, like IL-10 and single Ig IL-1–related receptor (62). Protective functions of DCs have also been shown in models of drug-induced tubulotoxicity (63) and acute crescentic GN (64), which may be mediated through the inducible costimulatory ligand on DCs (65), a T-cell suppressor. However, these studies have to be interpreted with caution, because they were obtained with the use of experimental techniques that may be associated with systemic neutrophilia as a side effect (66). Some studies may need to be revisited to clarify an influence of side effects.

After acute injury, both DCs and CSF-1–dependent macrophages orchestrated tissue repair by producing mediators like IL-22 (67,68), suggesting novel therapeutic avenues in both transplantation and acute tubular necrosis.

Chronic Progression of GN
Persistent signaling through pattern-sensing receptors causes resident DCs to mature and become proinflammatory. Furthermore, chronic kidney inflammation attracts circulatory monocytes through chemokines. These differentiate within the kidney into DCs and macrophages with proinflammatory functionality, which progressively replace resident immature DCs. Thus, the renal environment turns more and more proinflammatory and supportive of CKD progression. This functional change has been described in murine models of crescentic GN (40) and lupus nephritis (69). Matured DCs stimulated T helper cells, which produced cytokines like IFN-γ to activate renal macrophages to mediate kidney damage (Figure 2C), consistent with a type IV delayed type hypersensitivity reaction (70). This immune cell cross-talk may be the mechanistic explanation for the well known mononuclear periglomerular infiltrates regularly observed in many forms of GN (71). It is well established that the extent of tubulointerstitial mononuclear infiltration correlates with the kidney function and its prognosis in many types of CKD, including those not primarily by the immune system (like diabetic or hypertensive nephropathy) (71), suggesting a general role of tubulointerstitial immune cell cross-talk in CKD progression. Thus, the histopathologic diagnosis of nephritis may be advanced by considering functional parameters, like the DC maturation state (72), the T cell cytokine production, or macrophage activation.

Role in Lupus Nephritis
Immune cell cross-talk is also important in lupus nephritis, a renal manifestation of a systemic immune disorder resulting from a defect in the homeostatic clearance of apoptotic
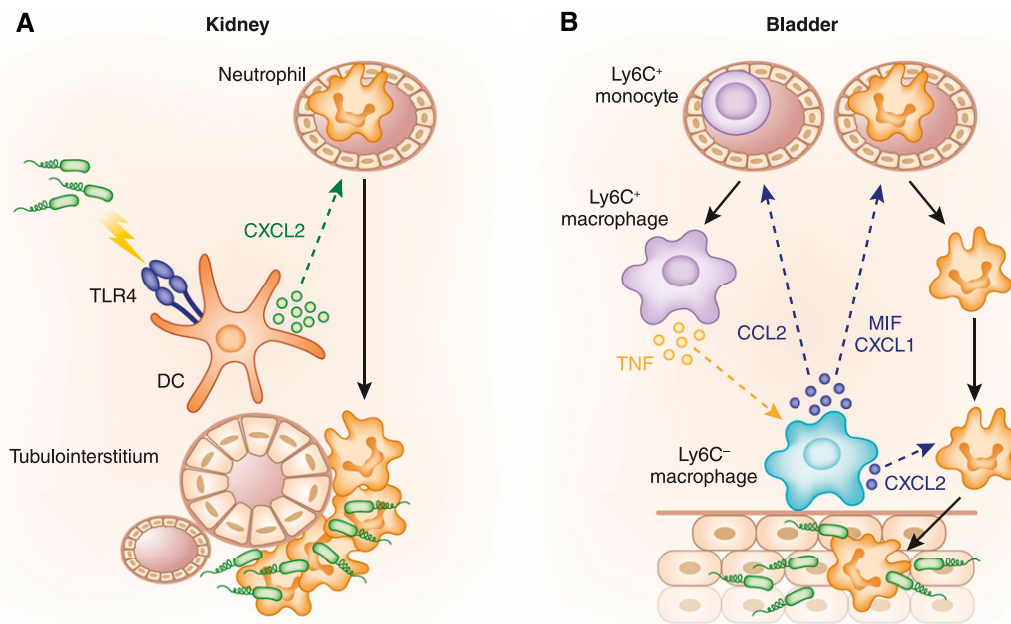
Figure 4. | Immune response against urinary tract infection. (A) In bacterial pyelonephritis, ascending uropathogenic *E. coli* (green) is sensed by Toll-like receptor (TLR) -expressing kidney DCs positioned in the medulla adjacent to collecting ducts and tubules. Medullary DCs respond by secreting CXCL2 that attracts neutrophils to eliminate the bacteria. (B) In bacterial cystitis, resident Ly6C⁻ sentinel macrophages sense uropathogenic *E. coli* and start secreting chemokines to recruit circulatory neutrophils and Ly6C⁺ monocytes. The latter differentiates into Ly6C⁺ helper macrophages that release TNF as helper signal, which enables Ly6C⁻ sentinel macrophages to produce additional chemokines to guide neutrophils into the frontline of infection (the uroepithelium) to combat the bacteria. MIF, macrophage migration inhibitory factor.

cells (73), sensing of the accumulating self-nucleic acids that mimic a viral infection (74), and the ensuing loss of immune tolerance to nuclear autoantigens (75,76). In addition to mDCs, pDCs also play an important role in this condition by sensing nucleic acids antigens using TLR7 and TLR9 and driving intrarenal inflammation by secretion of type 1 IFN (74). Lupus nephritis is one of two conditions in which DCs infiltrates in glomeruli have been described (77), the other one being ANCA-associated GN (78).

Role in Nonimmune CKD

DCs play a minor role in CKD driven by mechanic or toxic injurious mediators. The best studied example is unilateral ureteral obstruction, the standard kidney fibrosis model. Although both DCs and macrophages showed signs of activation, only the removal of macrophages (but not DCs) attenuated kidney fibrosis (79,80). The important functional role of macrophages explains the correlation between their intrarenal numbers and the severity of fibrosis in human studies (81). Mechanistically, activated macrophages secreted reactive oxygen species and proinflammatory cytokines, which induced apoptosis of tubular epithelial cells and stimulated interstitial fibroblasts to deposit extracellular matrix, leading to kidney fibrosis (82,83). Several macrophage-activating receptors have been described with inhibition that may be of therapeutic value in nonimmune CKD (84–86) (Table 2).

Intrarenal Inflammasome Activation

Many forms of sterile inflammation are driven by inflammasome activation and important for the nephrologist,

usually lead to tissue fibrosis (34). The kidney is predisposed to inflammasome activation, because the concentration of the primary filtrate and the high osmolarity in the renal medulla favor crystal formation after the solubility coefficient of a given salt is exceeded within the tubular lumen (Figure 2A). Indeed, it has been reported that calcium oxalate crystals activate the inflammasome in renal DCs (87), which may cause progressive loss of kidney function over weeks (88). Additional examples of inflammasome-activating nephrotoxic crystals are formed by uric acid (resulting in gout nephropathy) and adenine (89), which is released, for example, during chemotherapy. Experimental studies have also shown a role of the inflammasome in IRI (90) and unilateral ureter ligation (91). Numerous stimuli other than crystals have been reported to trigger the inflammasome, but it is unclear which of them are important in these conditions. Regardless of the underlying reasons, inhibition of the inflammasome product, IL-1, has recently been used successfully in many forms of sterile inflammation (92), albeit not yet in those affecting the kidney. Furthermore, small molecular weight inhibitors of the inflammasome itself are currently being developed and tested. Finally, it might be possible to prevent inflammasome activation by targeting the renal cells in which it is expressed (the DCs and macrophages).

Kidney Transplantation

Renal allograft rejection results from the recognition of graft antigens that provoke an immune response of the recipient (93). DCs are central to both the direct and indirect allorecognition pathways, where donor antigens are presented

to recipient T cells by donor or recipient DCs, respectively. Direct recognition may contribute to acute allograft rejection (94), whereas indirect recognition causes chronic allograft rejection and alloantibody formation (95). This is logical, because recipient B cells need to receive recipient T-cell help, which can be stimulated only by recipient DCs. Donor DCs possess a limited half-life and can contribute to rejection only in the acute phase. During that phase, donor DCs are exposed to IRI-mediated damage that renders them particularly stimulatory. IRI can be studied in animals much more easily than full organ transplantation, and therefore, abundant information is available on the molecular mechanism of IRI, showing, for example, the potent production of proinflammatory cytokines (59). Consistently, the analysis of human kidney biopsies showed that a strong mDC influx during acute rejection predicts a poor outcome (96).

Therapeutic Manipulation of Renal DCs and Macrophages

Adoptive Transfer of DCs and Macrophages

The transfer of tolerogenic donor-derived immature DCs before kidney transplantation seems to be a promising therapeutic strategy to prevent proinflammatory functions of kidney passenger DCs. Such donor DCs can promote alloantigen-specific T-cell unresponsiveness and transplant survival (97). Inhibition of T effector cells and induction of regulatory T cells were observed in volunteers treated with DCs (98,99). These effects may be augmented by immunosuppressive therapies (100).

Transfer of activated macrophages as Ehrlich's magic bullets that migrate into sites of inflammation has been shown to aggravate kidney disease (101), consistent with the proinflammatory function of these cells. By contrast, the transfer of macrophages genetically modified to express immunosuppressive mediators attenuated inflammatory kidney disease (102,103). It remains to be seen whether such genetic modifications are stable and safe enough for therapeutic use in humans.

Removal of DCs and Macrophages

The depletion of renal DCs and macrophages is the most straightforward approach to prevent their disease-aggravating effects in CKD. In animals, this can be achieved with the use of clodronate liposomes, which are not specific for DCs or macrophages. More specific are the numerous transgenic tools previously used *in vivo* for loss-of-function experiments, which allow determination of how disease models develop in the absence of DCs and/or macrophages. However, current techniques do not permit their selective removal from the kidney to preserve their anti-infectious activity in other organs. Additionally, it is unclear whether the ensuing side effects would be tolerable in humans.

Preventing DCs and Macrophage Recruitment

DC and macrophage recruitment into the inflamed kidney can be inhibited by blocking the chemokine receptors involved. The receptor CX_3CR1 mediates the homeostatic colonization of the kidney (but not other organs) with DCs, except the intestine (40). Therefore, CX_3CR1 should represent a highly desirable therapeutic target, because its inhibition should entail fewer side effects in other organs. However, under inflammatory conditions, CX_3CR1 is not the only receptor mediating monocyte recruitment; also, CCR1, CCR2, and CCR5 have been implicated (104,105). It remains to be seen whether and how much these receptors can compensate when CX_3CR1 is blocked. Particularly, CCR2 is important for proinflammatory macrophages, and its inhibition (or inhibition of its ligand CCL2) was effective in mouse models of unilateral ureter ligation (79), lupus nephritis (106), ischemia/reperfusion (107), and diabetic nephropathy (108). Chemokine receptors can be targeted well by small molecular weight drugs; some of these are currently under investigation, but their value for treating kidney disease is unclear at present. Finally, some immunosuppressive drugs, such as laquinimod, have been shown to reduce chemokine secretion and immune cell infiltration in other tissues and may be of use in nephritis (109).

Preventing DC Maturation and Macrophage Activation

Another promising approach is to inhibit DC maturation, the prerequisite for their ability to aggravate chronic disease. An obvious candidate is the transcription factor NF-κB, a master regulator of immune cell activation, which offers the additional advantage of also being active in two additional main components of renal mononuclear infiltrates (T helper cells and macrophages). NF-κB inhibitors have been used successfully in several immune-mediated diseases, including SLE (110), but have not yet been used successfully in primary CKDs. Interestingly, the effectivity of type I angiotensin receptor blockade in CKD is partially mediated through inhibition of macrophages, which express this receptor as well (111). Table 2 lists additional receptors important in CKD with the potential to modify DC or macrophage activation. Some of the immunosuppressive agents used to prevent transplant rejection prevented DC activation *in vitro* (for example, sirolimus [112] and tacrolimus [113]). However, their usefulness in CKD is limited by side effects. Finally, the numerous recent inhibitors of proinflammatory cytokines produced by DCs and macrophages possess therapeutic potential, but these drugs will be discussed in another review of this series.

References

1. Gordon S: Alternative activation of macrophages. *Nat Rev Immunol* 3: 23–35, 2003
2. Steinman RM, Cohn ZA: Identification of a novel cell type in peripheral lymphoid organs of mice. I. Morphology, quantitation, tissue distribution. *J Exp Med* 137: 1142–1162, 1973
3. Banchereau J, Steinman RM: Dendritic cells and the control of immunity. *Nature* 392: 245–252, 1998
4. Kurts C, Robinson BW, Knolle PA: Cross-priming in health and disease. *Nat Rev Immunol* 10: 403–414, 2010
5. Heath WR, Carbone FR: Dendritic cell subsets in primary and secondary T cell responses at body surfaces. *Nat Immunol* 10: 1237–1244, 2009
6. Merad M, Sathe P, Helft J, Miller J, Mortha A: The dendritic cell lineage: Ontogeny and function of dendritic cells and their subsets in the steady state and the inflamed setting. *Annu Rev Immunol* 31: 563–604, 2013

7. Guilliams M, Henri S, Tamoutounour S, Ardouin L, Schwartz-Cornil I, Dalod M, Malissen B: From skin dendritic cells to a simplified classification of human and mouse dendritic cell subsets. *Eur J Immunol* 40: 2089–2094, 2010

8. Hashimoto D, Chow A, Noizat C, Teo P, Beasley MB, Leboeuf M, Becker CD, See P, Price J, Lucas D, Greter M, Mortha A, Boyer SW, Forsberg EC, Tanaka M, van Rooijen N, García-Sastre A, Stanley ER, Ginhoux F, Frenette PS, Merad M: Tissue-resident macrophages self-maintain locally throughout adult life with minimal contribution from circulating monocytes. *Immunity* 38: 792–804, 2013

9. Mildner A, Jung S: Development and function of dendritic cell subsets. *Immunity* 40: 642–656, 2014

10. Geissmann F, Manz MG, Jung S, Sieweke MH, Merad M, Ley K: Development of monocytes, macrophages, and dendritic cells. *Science* 327: 656–661, 2010

11. Collin M, McGovern N, Haniffa M: Human dendritic cell subsets. *Immunology* 140: 22–30, 2013

12. Gordon S, Taylor PR: Monocyte and macrophage heterogeneity. *Nat Rev Immunol* 5: 953–964, 2005

13. Wang Y, Harris DC: Macrophages in renal disease. *J Am Soc Nephrol* 22: 21–27, 2011

14. Huen SC, Cantley LG: Macrophage-mediated injury and repair after ischemic kidney injury [published online ahead of print January 19, 2014]. *Pediatr Nephrol*

15. Ivashkiv LB: Epigenetic regulation of macrophage polarization and function. *Trends Immunol* 34: 216–223, 2013

16. Schiwon M, Weisheit C, Franken L, Gutweiler S, Dixit A, Meyer-Schwesinger C, Pohl JM, Maurice NJ, Thiebes S, Lorenz K, Quast T, Fuhrmann M, Baumgarten G, Lohse MJ, Opdenakker G, Bernhagen J, Bucala R, Panzer U, Kolanus W, Gröne HJ, Garbi N, Kastenmüller W, Knolle PA, Kurts C, Engel DR: Crosstalk between sentinel and helper macrophages permits neutrophil migration into infected uroepithelium. *Cell* 156: 456–468, 2014

17. Geissmann F, Jung S, Littman DR: Blood monocytes consist of two principal subsets with distinct migratory properties. *Immunity* 19: 71–82, 2003

18. Auffray C, Fogg D, Garfa M, Elain G, Join-Lambert O, Kayal S, Sarnacki S, Cumano A, Lauvau G, Geissmann F: Monitoring of blood vessels and tissues by a population of monocytes with patrolling behavior. *Science* 317: 666–670, 2007

19. Carlin LM, Stamatiades EG, Auffray C, Hanna RN, Glover L, Vizcay-Barrena G, Hedrick CC, Cook HT, Diebold S, Geissmann F: Nr4a1-dependent Ly6C(low) monocytes monitor endothelial cells and orchestrate their disposal. *Cell* 153: 362–375, 2013

20. Xue J, Schmidt SV, Sander J, Draffehn A, Krebs W, Quester I, De Nardo D, Gohel TD, Emde M, Schmidleithner L, Ganesan H, Nino-Castro A, Mallmann MR, Labzin L, Theis H, Kraut M, Beyer M, Latz E, Freeman TC, Ulas T, Schultze JL: Transcriptome-based network analysis reveals a spectrum model of human macrophage activation. *Immunity* 40: 274–288, 2014

21. Wynn TA, Chawla A, Pollard JW: Macrophage biology in development, homeostasis and disease. *Nature* 496: 445–455, 2013

22. Schulz C, Gomez Perdiguero E, Chorro L, Szabo-Rogers H, Cagnard N, Kierdorf K, Prinz M, Wu B, Jacobsen SE, Pollard JW, Frampton J, Liu KJ, Geissmann F: A lineage of myeloid cells independent of Myb and hematopoietic stem cells. *Science* 336: 86–90, 2012

23. Ginhoux F, Jung S: Monocytes and macrophages: Developmental pathways and tissue homeostasis. *Nat Rev Immunol* 14: 392–404, 2014

24. Davies LC, Jenkins SJ, Allen JE, Taylor PR: Tissue-resident macrophages. *Nat Immunol* 14: 986–995, 2013

25. Davies LC, Rosas M, Jenkins SJ, Liao CT, Scurr MJ, Brombacher F, Fraser DJ, Allen JE, Jones SA, Taylor PR: Distinct bone marrow-derived and tissue-resident macrophage lineages proliferate at key stages during inflammation. *Nat Commun* 4: 1886, 2013

26. Krüger T, Benke D, Eitner F, Lang A, Wirtz M, Hamilton-Williams EE, Engel D, Giese B, Müller-Newen G, Floege J, Kurts C: Identification and functional characterization of dendritic cells in the healthy murine kidney and in experimental glomerulonephritis. *J Am Soc Nephrol* 15: 613–621, 2004

27. Nelson PJ, Rees AJ, Griffin MD, Hughes J, Kurts C, Duffield J: The renal mononuclear phagocytic system. *J Am Soc Nephrol* 23: 194–203, 2012

28. Steinman RM, Idoyaga J: Features of the dendritic cell lineage. *Immunol Rev* 234: 5–17, 2010

29. Leemans JC, Stokman G, Claessen N, Rouschop KM, Teske GJ, Kirschning CJ, Akira S, van der Poll T, Weening JJ, Florquin S: Renal-associated TLR2 mediates ischemia/reperfusion injury in the kidney. *J Clin Invest* 115: 2894–2903, 2005

30. Wu H, Chen G, Wyburn KR, Yin J, Bertolino P, Eris JM, Alexander SI, Sharland AF, Chadban SJ: TLR4 activation mediates kidney ischemia/reperfusion injury. *J Clin Invest* 117: 2847–2859, 2007

31. Allam R, Scherbaum CR, Darisipudi MN, Mulay SR, Hägele H, Lichtnekert J, Hagemann JH, Rupanagudi KV, Ryu M, Schwarzenberger C, Hohenstein B, Hugo C, Uhl B, Reichel CA, Krombach F, Monestier M, Liapis H, Moreth K, Schaefer L, Anders HJ: Histones from dying renal cells aggravate kidney injury via TLR2 and TLR4. *J Am Soc Nephrol* 23: 1375–1388, 2012

32. Geijtenbeek TB, Gringhuis SI: Signalling through C-type lectin receptors: Shaping immune responses. *Nat Rev Immunol* 9: 465–479, 2009

33. Bauernfeind F, Hornung V: Of inflammasomes and pathogens—sensing of microbes by the inflammasome. *EMBO Mol Med* 5: 814–826, 2013

34. Rock KL, Latz E, Ontiveros F, Kono H: The sterile inflammatory response. *Annu Rev Immunol* 28: 321–342, 2010

35. Leemans JC, Kors L, Anders HJ, Florquin S: Pattern recognition receptors and the inflammasome in kidney disease. *Nat Rev Nephrol* 10: 398–414, 2014

36. Soos TJ, Sims TN, Barisoni L, Lin K, Littman DR, Dustin ML, Nelson PJ: CX3CR1+ interstitial dendritic cells form a contiguous network throughout the entire kidney. *Kidney Int* 70: 591–596, 2006

37. Hume DA: Applications of myeloid-specific promoters in transgenic mice support in vivo imaging and functional genomics but do not support the concept of distinct macrophage and dendritic cell lineages or roles in immunity. *J Leukoc Biol* 89: 525–538, 2011

38. Kawakami T, Lichtnekert J, Thompson LJ, Karna P, Bouabe H, Hohl TM, Heinecke JW, Ziegler SF, Nelson PJ, Duffield JS: Resident renal mononuclear phagocytes comprise five discrete populations with distinct phenotypes and functions. *J Immunol* 191: 3358–3372, 2013

39. Schwarz M, Taubitz A, Eltrich N, Mulay SR, Allam R, Vielhauer V: Analysis of TNF-mediated recruitment and activation of glomerular dendritic cells in mouse kidneys by compartment-specific flow cytometry. *Kidney Int* 84: 116–129, 2013

40. Hochheiser K, Heuser C, Krause TA, Teteris S, Ilias A, Weisheit C, Hoss F, Tittel AP, Knolle PA, Panzer U, Engel DR, Tharaux PL, Kurts C: Exclusive CX3CR1 dependence of kidney DCs impacts glomerulonephritis progression. *J Clin Invest* 123: 4242–4254, 2013

41. Ginhoux F, Liu K, Helft J, Bogunovic M, Greter M, Hashimoto D, Price J, Yin N, Bromberg J, Lira SA, Stanley ER, Nussenzweig M, Merad M: The origin and development of nonlymphoid tissue CD103+ DCs. *J Exp Med* 206: 3115–3130, 2009

42. Schreiner GF, Kiely JM, Cotran RS, Unanue ER: Characterization of resident glomerular cells in the rat expressing Ia determinants and manifesting genetically restricted interactions with lymphocytes. *J Clin Invest* 68: 920–931, 1981

43. Kaissling B, Le Hir M: Characterization and distribution of interstitial cell types in the renal cortex of rats. *Kidney Int* 45: 709–720, 1994

44. Kaissling B, Hegyi I, Loffing J, Le Hir M: Morphology of interstitial cells in the healthy kidney. *Anat Embryol (Berl)* 193: 303–318, 1996

45. Schraml BU, van Blijswijk J, Zelenay S, Whitney PG, Filby A, Acton SE, Rogers NC, Moncaut N, Carvajal JJ, Reis e Sousa C: Genetic tracing via DNGR-1 expression history defines dendritic cells as a hematopoietic lineage. *Cell* 154: 843–858, 2013

46. Woltman AM, de Fijter JW, Zuidwijk K, Vlug AG, Bajema IM, van der Kooij SW, van Ham V, van Kooten C: Quantification of dendritic cell subsets in human renal tissue under normal and pathological conditions. *Kidney Int* 71: 1001–1008, 2007

47. Segerer S, Heller F, Lindenmeyer MT, Schmid H, Cohen CD, Draganovici D, Mandelbaum J, Nelson PJ, Gröne HJ, Gröne EF, Figel AM, Nössner E, Schlöndorff D: Compartment specific

expression of dendritic cell markers in human glomerulonephritis. *Kidney Int* 74: 37–46, 2008

48. Ferenbach D, Hughes J: Macrophages and dendritic cells: What is the difference? *Kidney Int* 74: 5–7, 2008

49. Rogers NM, Matthews TJ, Kausman JY, Kitching AR, Coates PT: Review article: Kidney dendritic cells: Their role in homeostasis, inflammation and transplantation. *Nephrology (Carlton)* 14: 625–635, 2009

50. Lukacs-Kornek V, Engel D, Tacke F, Kurts C: The role of chemokines and their receptors in dendritic cell biology. *Front Biosci* 13: 2238–2252, 2008

51. Chieppa M, Rescigno M, Huang AY, Germain RN: Dynamic imaging of dendritic cell extension into the small bowel lumen in response to epithelial cell TLR engagement. *J Exp Med* 203: 2841–2852, 2006

52. Gottschalk C, Damuzzo V, Gotot J, Kroczek RA, Yagita H, Murphy KM, Knolle PA, Ludwig-Portugall I, Kurts C: Batf3-dependent dendritic cells in the renal lymph node induce tolerance against circulating antigens. *J Am Soc Nephrol* 24: 543–549, 2013

53. Patole PS, Schubert S, Hildinger K, Khandoga S, Khandoga A, Segerer S, Henger A, Kretzler M, Werner M, Krombach F, Schlöndorff D, Anders HJ: Toll-like receptor-4: Renal cells and bone marrow cells signal for neutrophil recruitment during pyelonephritis. *Kidney Int* 68: 2582–2587, 2005

54. Abbas AK: Die and let live: Eliminating dangerous lymphocytes. *Cell* 84: 655–657, 1996

55. Tittel AP, Heuser C, Ohliger C, Knolle PA, Engel DR, Kurts C: Kidney dendritic cells induce innate immunity against bacterial pyelonephritis. *J Am Soc Nephrol* 22: 1435–1441, 2011

56. Lionakis MS, Swamydas M, Fischer BG, Plantinga TS, Johnson MD, Jaeger M, Green NM, Masedunskas A, Weigert R, Mikelis C, Wan W, Lee CC, Lim JK, Rivollier A, Yang JC, Laird GM, Wheeler RT, Alexander BD, Perfect JR, Gao JL, Kullberg BJ, Netea MG, Murphy PM: CX3CR1-dependent renal macrophage survival promotes Candida control and host survival. *J Clin Invest* 123: 5035–5051, 2013

57. Keane J, Gershon S, Wise RP, Mirabile-Levens E, Kasznica J, Schwieterman WD, Siegel JN, Braun MM: Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med* 345: 1098–1104, 2001

58. Anders HJ: Immune system modulation of kidney regeneration—mechanisms and implications. *Nat Rev Nephrol* 10: 347–358, 2014

59. Dong X, Swaminathan S, Bachman LA, Croatt AJ, Nath KA, Griffin MD: Antigen presentation by dendritic cells in renal lymph nodes is linked to systemic and local injury to the kidney. *Kidney Int* 68: 1096–1108, 2005

60. Kim MG, Boo CS, Ko YS, Lee HY, Cho WY, Kim HK, Jo SK: Depletion of kidney CD11c+ F4/80+ cells impairs the recovery process in ischaemia/reperfusion-induced acute kidney injury. *Nephrol Dial Transplant* 25: 2908–2921, 2010

61. Cho WY, Choi HM, Lee SY, Kim MG, Kim HK, Jo SK: The role of Tregs and CD11c(+) macrophages/dendritic cells in ischemic preconditioning of the kidney. *Kidney Int* 78: 981–992, 2010

62. Lech M, Avila-Ferrufino A, Allam R, Segerer S, Khandoga A, Krombach F, Garlanda C, Mantovani A, Anders HJ: Resident dendritic cells prevent postischemic acute renal failure by help of single Ig IL-1 receptor-related protein. *J Immunol* 183: 4109–4118, 2009

63. Tadagavadi RK, Reeves WB: Renal dendritic cells ameliorate nephrotoxic acute kidney injury. *J Am Soc Nephrol* 21: 53–63, 2010

64. Scholz J, Lukacs-Kornek V, Engel DR, Specht S, Kiss E, Eitner F, Floege J, Groene HJ, Kurts C: Renal dendritic cells stimulate IL-10 production and attenuate nephrotoxic nephritis. *J Am Soc Nephrol* 19: 527–537, 2008

65. Odobasic D, Kitching AR, Semple TJ, Holdsworth SR: Inducible co-stimulatory molecule ligand is protective during the induction and effector phases of crescentic glomerulonephritis. *J Am Soc Nephrol* 17: 1044–1053, 2006

66. Tittel AP, Heuser C, Ohliger C, Llanto C, Yona S, Hämmerling GJ, Engel DR, Garbi N, Kurts C: Functionally relevant neutrophilia in CD11c diphtheria toxin receptor transgenic mice. *Nat Methods* 9: 385–390, 2012

67. Kulkarni OP, Hartter I, Mulay SR, Hagemann J, Darisipudi MN, Kumar Vr S, Romoli S, Thomasova D, Ryu M, Kobold S, Anders HJ: Toll-like receptor 4-induced IL-22 accelerates kidney regeneration. *J Am Soc Nephrol* 25: 978–989, 2014

68. Zhang MZ, Yao B, Yang S, Jiang L, Wang S, Fan X, Yin H, Wong K, Miyazawa T, Chen J, Chang I, Singh A, Harris RC: CSF-1 signaling mediates recovery from acute kidney injury. *J Clin Invest* 122: 4519–4532, 2012

69. Castellano G, Trouw LA, Fiore N, Daha MR, Schena FP, van Kooten C: Infiltrating dendritic cells contribute to local synthesis of C1q in murine and human lupus nephritis. *Mol Immunol* 47: 2129–2137, 2010

70. Holdsworth SR, Tipping PG: Leukocytes in glomerular injury. *Semin Immunopathol* 29: 355–374, 2007

71. Bohle A, Kressel G, Müller CA, Müller GA: The pathogenesis of chronic renal failure. *Pathol Res Pract* 185: 421–440, 1989

72. Kassianos AJ, Wang X, Sampangi S, Muczynski K, Healy H, Wilkinson R: Increased tubulointerstitial recruitment of human CD141(hi) CLEC9A(+) and CD1c(+) myeloid dendritic cell subsets in renal fibrosis and chronic kidney disease. *Am J Physiol Renal Physiol* 305: F1391–F1401, 2013

73. Bosch X: Systemic lupus erythematosus and the neutrophil. *N Engl J Med* 365: 758–760, 2011

74. Theofilopoulos AN, Baccala R, Beutler B, Kono DH: Type I interferons (alpha/beta) in immunity and autoimmunity. *Annu Rev Immunol* 23: 307–336, 2005

75. Liu Z, Davidson A: Taming lupus-a new understanding of pathogenesis is leading to clinical advances. *Nat Med* 18: 871–882, 2012

76. Tsokos GC: Systemic lupus erythematosus. *N Engl J Med* 365: 2110–2121, 2011

77. Tucci M, Quatraro C, Lombardi L, Pellegrino C, Dammacco F, Silvestris F: Glomerular accumulation of plasmacytoid dendritic cells in active lupus nephritis: Role of interleukin-18. *Arthritis Rheum* 58: 251–262, 2008

78. Wilde B, van Paassen P, Damoiseaux J, Heerings-Rewinkel P, van Rie H, Witzke O, Tervaert JW: Dendritic cells in renal biopsies of patients with ANCA-associated vasculitis. *Nephrol Dial Transplant* 24: 2151–2156, 2009

79. Kitagawa K, Wada T, Furuichi K, Hashimoto H, Ishiwata Y, Asano M, Takeya M, Kuziel WA, Matsushima K, Mukaida N, Yokoyama H: Blockade of CCR2 ameliorates progressive fibrosis in kidney. *Am J Pathol* 165: 237–246, 2004

80. Snelgrove SL, Kausman JY, Lo C, Lo C, Ooi JD, Coates PT, Hickey MJ, Holdsworth SR, Kurts C, Engel DR, Kitching AR: Renal dendritic cells adopt a pro-inflammatory phenotype in obstructive uropathy to activate T cells but do not directly contribute to fibrosis. *Am J Pathol* 180: 91–103, 2012

81. Eddy AA: Interstitial macrophages as mediators of renal fibrosis. *Exp Nephrol* 3: 76–79, 1995

82. Misseri R, Meldrum DR, Dinarello CA, Dagher P, Hile KL, Rink RC, Meldrum KK: TNF-alpha mediates obstruction-induced renal tubular cell apoptosis and proapoptotic signaling. *Am J Physiol Renal Physiol* 288: F406–F411, 2005

83. Zeisberg EM, Potenta SE, Sugimoto H, Zeisberg M, Kalluri R: Fibroblasts in kidney fibrosis emerge via endothelial-to-mesenchymal transition. *J Am Soc Nephrol* 19: 2282–2287, 2008

84. Ma LJ, Corsa BA, Zhou J, Yang H, Li H, Tang YW, Babaev VR, Major AS, Linton MF, Fazio S, Hunley TE, Kon V, Fogo AB: Angiotensin type 1 receptor modulates macrophage polarization and renal injury in obesity. *Am J Physiol Renal Physiol* 300: F1203–F1213, 2011

85. Ge S, Hertel B, Susnik N, Rong S, Dittrich AM, Schmitt R, Haller H, von Vietinghoff S: Interleukin 17 receptor A modulates monocyte subsets and macrophage generation in vivo. *PLoS ONE* 9: e85461, 2014

86. Lo TH, Tseng KY, Tsao WS, Yang CY, Hsieh SL, Chiu AW, Takai T, Mak TW, Tarng DC, Chen NJ: TREM-1 regulates macrophage polarization in ureteral obstruction [published online ahead of print June 11, 2014]. *Kidney Int* doi:10.1038/ki.2014.205

87. Mulay SR, Kulkarni OP, Rupanagudi KV, Migliorini A, Darisipudi MN, Vilaysane A, Muruve D, Shi Y, Munro F, Liapis H, Anders HJ: Calcium oxalate crystals induce renal inflammation by NLRP3-mediated IL-1β secretion. *J Clin Invest* 123: 236–246, 2013

88. Knauf F, Asplin JR, Granja I, Schmidt IM, Moeckel GW, David RJ, Flavell RA, Aronson PS: NALP3-mediated inflammation is a principal cause of progressive renal failure in oxalate nephropathy. *Kidney Int* 84: 895–901, 2013

89. Correa-Costa M, Braga TT, Semedo P, Hayashida CY, Bechara LR, Elias RM, Barreto CR, Silva-Cunha C, Hyane MI, Gonçalves GM, Brum PC, Fujihara C, Zatz R, Pacheco-Silva A, Zamboni DS, Camara NO: Pivotal role of Toll-like receptors 2 and 4, its adaptor molecule MyD88, and inflammasome complex in experimental tubule-interstitial nephritis. *PLoS ONE* 6: e29004, 2011

90. Kim HJ, Lee DW, Ravichandran K, O Keys D, Akcay A, Nguyen Q, He Z, Jani A, Ljubanovic D, Edelstein CL: NLRP3 inflammasome knockout mice are protected against ischemic but not cisplatin-induced acute kidney injury. *J Pharmacol Exp Ther* 346: 465–472, 2013

91. Vilaysane A, Chun J, Seamone ME, Wang W, Chin R, Hirota S, Li Y, Clark SA, Tschopp J, Trpkov K, Hemmelgarn BR, Beck PL, Muruve DA: The NLRP3 inflammasome promotes renal inflammation and contributes to CKD. *J Am Soc Nephrol* 21: 1732–1744, 2010

92. Dinarello CA: IL-1: Discoveries, controversies and future directions. *Eur J Immunol* 40: 599–606, 2010

93. Sayegh MH: Why do we reject a graft? Role of indirect allorecognition in graft rejection. *Kidney Int* 56: 1967–1979, 1999

94. Garrod KR, Liu FC, Forrest LE, Parker I, Kang SM, Cahalan MD: NK cell patrolling and elimination of donor-derived dendritic cells favor indirect alloreactivity. *J Immunol* 184: 2329–2336, 2010

95. Dong VM, Womer KL, Sayegh MH: Transplantation tolerance: The concept and its applicability. *Pediatr Transplant* 3: 181–192, 1999

96. Zuidwijk K, de Fijter JW, Mallat MJ, Eikmans M, van Groningen MC, Goemaere NN, Bajema IM, van Kooten C: Increased influx of myeloid dendritic cells during acute rejection is associated with interstitial fibrosis and tubular atrophy and predicts poor outcome. *Kidney Int* 81: 64–75, 2012

97. Moreau A, Varey E, Bouchet-Delbos L, Cuturi MC: Cell therapy using tolerogenic dendritic cells in transplantation. *Transp Res* 1: 13, 2012

98. Dhodapkar MV, Steinman RM: Antigen-bearing immature dendritic cells induce peptide-specific CD8(+) regulatory T cells in vivo in humans. *Blood* 100: 174–177, 2002

99. Dhodapkar MV, Steinman RM, Krasovsky J, Munz C, Bhardwaj N: Antigen-specific inhibition of effector T cell function in humans after injection of immature dendritic cells. *J Exp Med* 193: 233–238, 2001

100. Xia MJ, Shan J, Li YP, Zhou YN, Guo YJ, Sun GX, Wu WQ, Feng L: Adoptive transfusion of tolerant dendritic cells prolong the survival of renal allografts: A systematic review. *J Evid Based Med* 6: 250–264, 2013

101. Wang Y, Wang Y, Cao Q, Zheng G, Lee VW, Zheng D, Li X, Tan TK, Harris DC: By homing to the kidney, activated macrophages potently exacerbate renal injury. *Am J Pathol* 172: 1491–1499, 2008

102. Wilson HM, Chettibi S, Jobin C, Walbaum D, Rees AJ, Kluth DC: Inhibition of macrophage nuclear factor-kappaB leads to a dominant anti-inflammatory phenotype that attenuates glomerular inflammation in vivo. *Am J Pathol* 167: 27–37, 2005

103. Wilson HM, Stewart KN, Brown PA, Anegon I, Chettibi S, Rees AJ, Kluth DC: Bone-marrow-derived macrophages genetically modified to produce IL-10 reduce injury in experimental glomerulonephritis. *Mol Ther* 6: 710–717, 2002

104. Tacke F, Alvarez D, Kaplan TJ, Jakubzick C, Spanbroek R, Llodra J, Garin A, Liu J, Mack M, van Rooijen N, Lira SA, Habenicht AJ, Randolph GJ: Monocyte subsets differentially employ CCR2, CCR5, and CX3CR1 to accumulate within atherosclerotic plaques. *J Clin Invest* 117: 185–194, 2007

105. Vielhauer V, Kulkarni O, Reichel CA, Anders HJ: Targeting the recruitment of monocytes and macrophages in renal disease. *Semin Nephrol* 30: 318–333, 2010

106. Pérez de Lema G, Maier H, Franz TJ, Escribese M, Chilla S, Segerer S, Camarasa N, Schmid H, Banas B, Kalaydjiev S, Busch DH, Pfeffer K, Mampaso F, Schlöndorff D, Luckow B: Chemokine receptor Ccr2 deficiency reduces renal disease and prolongs survival in MRL/lpr lupus-prone mice. *J Am Soc Nephrol* 16: 3592–3601, 2005

107. Li L, Huang L, Sung SS, Vergis AL, Rosin DL, Rose CE Jr., Lobo PI, Okusa MD: The chemokine receptors CCR2 and CX3CR1 mediate monocyte/macrophage trafficking in kidney ischemia-reperfusion injury. *Kidney Int* 74: 1526–1537, 2008

108. Tesch GH: MCP-1/CCL2: A new diagnostic marker and therapeutic target for progressive renal injury in diabetic nephropathy. *Am J Physiol Renal Physiol* 294: F697–F701, 2008

109. Mishra MK, Wang J, Silva C, Mack M, Yong VW: Kinetics of proinflammatory monocytes in a model of multiple sclerosis and its perturbation by laquinimod. *Am J Pathol* 181: 642–651, 2012

110. Kalergis AM, Iruretagoyena MI, Barrientos MJ, González PA, Herrada AA, Leiva ED, Gutiérrez MA, Riedel CA, Bueno SM, Jacobelli SH: Modulation of nuclear factor-kappaB activity can influence the susceptibility to systemic lupus erythematosus. *Immunology* 128[Suppl]: e306–e314, 2009

111. Zhang JD, Patel MB, Griffiths R, Dolber PC, Ruiz P, Sparks MA, Stegbauer J, Jin H, Gomez JA, Buckley AF, Lefler WS, Chen D, Crowley SD: Type 1 angiotensin receptors on macrophages ameliorate IL-1 receptor-mediated kidney fibrosis. *J Clin Invest* 124: 2198–2203, 2014

112. Stallone G, Pontrelli P, Infante B, Gigante M, Netti GS, Ranieri E, Grandaliano G, Gesualdo L: Rapamycin induces ILT3(high)ILT4(high) dendritic cells promoting a new immunoregulatory pathway. *Kidney Int* 85: 888–897, 2014

113. Imai A, Sahara H, Tamura Y, Jimbow K, Saito T, Ezoe K, Yotsuyanagi T, Sato N: Inhibition of endogenous MHC class II-restricted antigen presentation by tacrolimus (FK506) via FKBP51. *Eur J Immunol* 37: 1730–1738, 2007

114. Dorner BG, Dorner MB, Zhou X, Opitz C, Mora A, Güttler S, Hutloff A, Mages HW, Ranke K, Schaefer M, Jack RS, Henn V, Kroczek RA: Selective expression of the chemokine receptor XCR1 on cross-presenting dendritic cells determines cooperation with CD8+ T cells. *Immunity* 31: 823–833, 2009

115. Nakano H, Yanagita M, Gunn MD: CD11c(+)B220(+)Gr-1(+) cells in mouse lymph nodes and spleen display characteristics of plasmacytoid dendritic cells. *J Exp Med* 194: 1171–1178, 2001

116. Patole PS, Pawar RD, Lech M, Zecher D, Schmidt H, Segerer S, Ellwart A, Henger A, Kretzler M, Anders HJ: Expression and regulation of Toll-like receptors in lupus-like immune complex glomerulonephritis of MRL-Fas(lpr) mice. *Nephrol Dial Transplant* 21: 3062–3073, 2006

117. Anders HJ, Vielhauer V, Eis V, Linde Y, Kretzler M, Perez de Lema G, Strutz F, Bauer S, Rutz M, Wagner H, Gröne HJ, Schlöndorff D: Activation of toll-like receptor-9 induces progression of renal disease in MRL-Fas(lpr) mice. *FASEB J* 18: 534–536, 2004

118. Day YJ, Huang L, Ye H, Linden J, Okusa MD: Renal ischemia-reperfusion injury and adenosine 2A receptor-mediated tissue protection: Role of macrophages. *Am J Physiol Renal Physiol* 288: F722–F731, 2005

119. Zhang G, Kim H, Cai X, Lopez-Guisa JM, Carmeliet P, Eddy AA: Urokinase receptor modulates cellular and angiogenic responses in obstructive nephropathy. *J Am Soc Nephrol* 14: 1234–1253, 2003