INTERNATIONAL JOURNAL OF Experimental Pathology

Int. J. Exp. Path. (2011), 92, 193–201

REVIEW ARTICLE

Kidney dendritic cells in acute and chronic renal disease

Katharina Hochheiser, André Tittel and Christian Kurts

Institute for Experimental Immunology, University Clinic of Bonn, Bonn, Germany

INTERNATIONAL JOURNAL OF EXPERIMENTAL PATHOLOGY

doi: 10.1111/j.1365-2613.2010.00728.x

Received for publication: 9 April 2010
Accepted for publication: 2 June 2010

Correspondence:
Christian Kurts
Institute of Experimental Immunology (IMMEI)
Friedrich-Wilhelms-Universität
53105 Bonn
Germany
Tel.: +49 228 287 11050
Fax: +49 228 287 11052
E-mail: ckurts@web.de
K.H and A.T. have contributed equally to this article.

Summary

Dendritic cells are not only the master regulators of adaptive immunity, but also participate profoundly in innate immune responses. Much has been learned about their basic immunological functions and their roles in various diseases. Comparatively little is still known about their role in renal disease, despite their obvious potential to affect immune responses in the kidney, and immune responses that are directed against renal components. Kidney dendritic cells form an abundant network in the renal tubulointerstitium and constantly survey the environment for signs of injury or infection, in order to alert the immune system to the need to initiate defensive action. Recent studies have identified a role for dendritic cells in several murine models of acute renal injury and chronic nephritis. Here we summarize the current knowledge on the role of kidney dendritic cells that has been obtained from the study of murine models of renal disease.

Keywords
cytokines, dendritic cells, glomerulonephritis

Dendritic cells (DCs) exist in all lymphatic and in nearly all non-lymphatic tissues (Steinman *et al.* 2003). As professional antigen presenting cells (APCs), their main task is the activation and regulation of T cells. Furthermore, they mediate the communication between the innate and the adaptive immune system (Steinman *et al.* 2005). DCs are specialized in taking up antigens in tissues, processing them and presenting them, after migration into lymphatic tissues, on MHC class I and II molecules to cytotoxic $CD8^+$ T cells (CTL) and $CD4^+$ T helper cells (Th cells) respectively. Depending on the activation status of the DCs, T cells become activated or are tolerized. That status results from recognition of pathogen-associated molecular patterns by means of a great variety of receptors, such as toll-like-receptors, that DCs use to sense whether an antigen was encountered in infectious or dangerous context. Various subsets of DCs exist that differ in their lineage, migratory properties, tissue distribution and their ability to activate Th cells and/or CTL. This complex topic has recently been reviewed elsewhere (Shortman & Naik 2007; Heath & Carbone 2009; Geissmann *et al.* 2010).

Relatively little is known about the role of DCs in renal diseases, despite abundant information on their roles in diseases affecting other organs. Cells with phenotypic characteristics of DCs have been described inside the kidneys of humans (Markovic-Lipkovski *et al.* 1990; Cuzic *et al.* 1992) and rodents more than 15 years ago (Austyn *et al.* 1994; Kaissling & Le Hir 1994; Roake *et al.* 1995; Kaissling *et al.* 1996). However, because of difficulties in identifying and in isolating these cells from the kidney, relatively little was known about their functional role until recently. Moreover, due to the expression of the F4/80-molecule, all APCs in the kidney were initially categorized as macrophages (Hume & Gordon 1983). However, F4/80 is specific for macrophages only in the spleen, whereas DCs in non-lymphoid tissues, including the kidney, express this marker too. Morphological and functional analysis showed that the tubulointerstitial stellate-shaped $F4/80^+$ cells mostly co-express the murine DC-marker CD11c and possess the functionality of conventional tissue DCs (Kruger *et al.* 2004). By confocal laser-microscopy it was shown that kidney dendritic cells (kDCs) form an extensive anatomic network that spans the entire

tubulointerstitium and encloses all nephrons (Soos *et al.* 2006). Functional investigations have revealed that kDCs in the steady-state maintain renal homeostasis (Kurts *et al.* 1997; Lukacs-Kornek *et al.* 2008). In transplantation, the tolerogenic properties of passenger leucocytes, most likely DCs, have long been known to induce a certain degree of transplantation tolerance (Ko *et al.* 1999). The role of renal DCs in transplantation has recently been reviewed elsewhere (Rogers *et al.* 2009). Studies in murine models of kidney diseases showed that kDCs accumulate in inflamed organs, secrete different cytokines and thereby either attenuate or aggravate renal injury (Figure 1). It is currently unclear why DCs are either anti- or pro-inflammatory, depending on the disease model used. In this review, we summarize the presently available knowledge on the functions of murine kDCs in the steady-state and in models of acute or chronic kidney injury.

Kidney DCs in the steady-state

Murine kDCs can be reliably identified by expression of both CD11c and MHC class II (one marker alone is insufficient). Most of them express the fractalkine receptor CX_3CR1 (Soos *et al.* 2006), F4/80 and the subtype marker CD11b at low levels (Kruger *et al.* 2004), which is characteristic of conventional tissue DCs (Table 1) (Shortman & Naik 2007; Merad *et al.* 2008; Heath & Carbone 2009; Geissmann *et al.* 2010). A subset of 5–15% shows the phenotype $CD11c^+$ $CD103^+$ ± $CD11b^-$ $F4/80^{LO}$ (Ginhoux *et al.* 2009), which characterizes tissue DCs related to the $CD8\alpha^+$ DCs in lymphatic tissues (Hildner *et al.* 2008). Their role in the kidney is unclear. Table 1 summarizes murine DC subsets that have been identified in the kidney.

kDCs have a turnover of about 14 days in homeostasis, as determined by bone marrow-transplantation experiments (Leszczynski *et al.* 1985; Dong *et al.* 2005). Tissue DCs may generally derive from circulating pre-DCs (proposed to give rise to the $CD103^+$ subset (Ginhoux *et al.* 2009)), from $Gr1^+$ inflammatory monocytes or $Gr1^{lo}$ 'patrolling' monocytes (Liu *et al.* 2007; Geissmann *et al.* 2010;). Both monocytes subsets are recruited to the inflamed kidney (Table 1) (Li *et al.* 2008) and can be identified within the organ by co-expression of CD11c, MHC class II and Gr1 (Heymann *et al.* 2009), until they downregulate Gr1. The DC precursor in the steady-state has not been identified yet.

Although experimental evidence for a functional role of the tubulointerstitial kDCs network is still quite limited, its location suggested early on that it may serve the surveillance of the renal parenchyma. The antigens captured by DCs within the kidney include tubular (Kurts *et al.* 1997; Dong *et al.* 2005;) and glomerular (Heymann *et al.* 2009) autoantigens, and small molecular weight antigens that are constitutively filtrated in glomeruli (Dong *et al.* 2005; Lukacs-Kornek *et al.* 2008). There is evidence that upon encountering maturation stimuli, kDCs migrate to the renal lymph nodes (Roake *et al.* 1995) where they activate specific T cells (Edgtton *et al.* 2008), consistent with the canonical life-cycle of DCs extrapolated from the paradigm of Langerhans cells in the skin (Steinman *et al.* 2003; Shortman & Naik 2007; Heath & Carbone 2009; Geissmann *et al.*

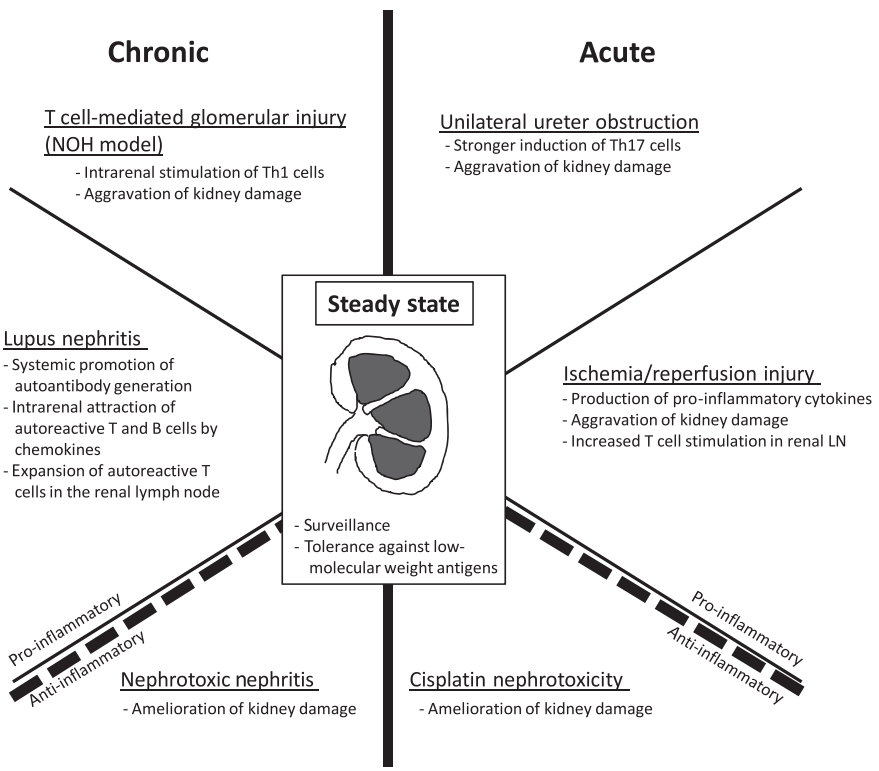

Figure 1 Functions of dendritic cells in various models of renal disease.

Table 1 Subsets of murine DCs

Murine DC subset Phenotype	Origin; presence in the kidney; functionality
DC subsets occurring in the kidney	
Conventional (myeloid) CD8$^-$ DC: CD11c$^+$ CD11b$^+$ CD8$^-$, F4/80$^+$ in tissues, in lymphatics DCIR$^+$	Likely pre-DC-derived, present in the kidney (Kruger *et al.* 2004); antigen transport from tissues to LNs, activation of Th cells
Conventional CD103$^+$ DC: CD11c$^+$ CD11b$^-$ CD8$^+$ CD103$^+$ CD205$^-$, Langerin$^+$	Pre-DC-derived, present in the kidney (Ginhoux *et al.* 2009); antigen transport from tissues to LNs, activation or tolerization of CD8$^+$ and CD4$^+$ T cells, cross-presentation
Inflammatory DC: CD11c$^+$ CD11b$^+$ CD8$^-$ F4/80$^+$ Gr-1$^+$	Monocyte-derived; present in the kidney (Heymann *et al.* 2009); proinflammatory functions and regulation of infiltrating Th cells
Plasmacytoid DC: CD11c^{int} CD11b$^-$ CD8$^-$ B220$^+$ Gr-1$^+$	Precursor distinct from that of conventional DCs; present in the human kidney (Woltman *et al.* 2007); produce IFN-α in viral infections
Follicular DC: CD11c$^-$ CD20$^-$ CD21$^+$ CD35$^+$	Probably not of haematopoietic origin; described only in Lupus nephritis (Turner *et al.* 2008); foster B cell responses
DC subsets not described in the kidney	
Conventional CD8$^+$ DC: CD11c$^+$ CD11b$^-$ CD8$^+$ CD205$^+$	Pre-DC-derived; present in lymphatic tissues only, reported in the renal LN (Scholz *et al.* 2008); activation of CD8$^+$ and CD4$^+$ T cells, cross-presentation
Langerhans cell: CD11c$^+$ CD11b$^+$ CD8$^-$ Langerin$^+$	Monocyte-derived; present in the skin only; transport antigen to cutaneous LNs, probably T cell activation

CD, cluster of differentiation; DC, dendritic cell; IFN, interferon; LN, lymph node; MR, mannose receptor.

2010). Additionally, small filterable antigens constitutively reach DCs resident in the renal lymph node by bulk drainage, and are captured there and, in the absence of pathogen-associated molecular patterns, are used to tolerize harmful T cells (Lukacs-Kornek *et al.* 2008). Such antigens may include food-derived antigens or autoantigens that are produced intermittently, like certain hormones, which are not readily available in the thymus for efficient negative selection of autoreactive T cells. The ability of the kidney to tolerize the immune system against innocuous small-molecular weight antigens may be of general relevance, but this notion remains to be formally demonstrated.

Kidney DCs in acute renal injury

Kidney DCs in ischaemia reperfusion injury

Ischaemia-reperfusion injury (IRI) is relevant especially for kidney transplantation. Early after ischaemic injury, kidney-resident F4/80$^+$ CD11c$^+$ DCs have been identified as the earliest source of TNF-α (Dong *et al.* 2005). Later, also hypoxic endothelial cells produced this cytokine (Schlichting *et al.* 2006). TNF-α caused influx of circulating immune cells, especially pro-inflammatory DC subsets, monocytes/macrophages and Th cells (Ysebaert *et al.* 2000), and directly contributed to kidney parenchymal damage. TNF-α receptors are expressed by many cells types, and upon ligation may initiate renal epithelial apoptosis (Dong *et al.* 2007).

Within 24 h following acute ischaemia, the T cell stimulatory capacity of kDCs increased markedly (Dong *et al.* 2005). Th cells have been demonstrated to aggravate IRI (Yokota *et al.* 2002; Burne-Taney *et al.* 2003; Ysebaert *et al.* 2004). T cells are important effectors also in other renal disease and in transplant rejection (Kurts *et al.* 2007; Rogers *et al.* 2009), suggesting that conditions of renal hypoxia might contribute to disease progression by activating kDCs to stimulate T cells. Indeed, hypoxia and the transcription factor HIF-1α have recently been shown to potently activate DC function when combined with LPS stimulation (Jantsch *et al.* 2008).

In contrast to these pro-inflammatory functions, myeloid cells of the kidney, likely kDC, have recently been proposed to attenuate IRI by production of single Ig IL-1-related receptor (SIGIRR) (Lech *et al.* 2009), an immunosuppressive mediator that attenuates also murine lupus models (discussed below) (Lech *et al.* 2008, 2010). Mice deficient for this mediator showed aggravated IRI. This could be reversed by treatment with clodronate liposomes (Clo-Lip), which effectively depletes phagocytic cells of the mononuclear phagocyte system from all tissues (Van Rooijen & Sanders 1994) including kDCs (Dong *et al.* 2005). It remains to be formally demonstrated that kDCs expressing SIGIRR actively suppress IRI and if so, how this may be reconciled with the pro-inflammatory TNF-α-mediated role of kDCs in IRI.

Kidney DCs in unilateral ureteral obstruction

The model of unilateral uretral obstruction (UUO) generates progressive renal fibrosis, which is considered a common feature of progressive renal diseases (Nagler 1973). The severity of fibrosis correlates with infiltration of activated macrophages (Eddy 1995), which secrete profibrotic and pro-inflammatory cytokines such as TGF-β and TNF-α respectively (Kitamoto *et al.* 2009). These macrophages induce apoptosis of tubular epithelial cells via TNF-α and TGF-β and produce reactive oxygen species that aggravate renal tubular injury (Misseri *et al.* 2005). Also endothelial cells undergo apoptosis, and renal fibroblasts differentiate

into myofibroblasts which promotes the deposition of extracellular matrix leading to fibrosis (Iwano *et al.* 2002; Zeisberg *et al.* 2008).

F4/80$^+$ kDCs are a potent source of TNF-α during the early stage of UUO (Dong *et al.* 2008). DC depletion with Clo-Lip attenuated obstruction-induced tubular apoptosis and renal fibrosis, and TNF-α and TGF-β were less elevated in obstructed kidneys (Kitamoto *et al.* 2009). T cells are thought to play a role in UUO as well, as evidenced by their accumulation at the cortico-medullary junction and in the cortex, where they colocalized with F4/80$^+$ kDCs (Dong *et al.* 2008). Although Clo-Lip treatment did not reduce the number of T cells, it attenuated their secretion of IFN-γ and IL-17 (Dong *et al.* 2008). However, it has recently been shown that Clo-Lip generally depletes renal F4/80$^+$ cells (Kitamoto *et al.* 2009), and hence not only DCs but also macrophages. Thus, although these findings clearly demonstrated that F4/80$^+$ phagocytes contribute to progressive renal fibrosis, it cannot be distinguished at present whether this was due to F4/80$^+$ macrophages and/or to F4/80$^+$ kDCs.

Kidney DCs in cisplatin nephrotoxicity

Renal tubular cells are particularly susceptible to toxic damage, for example in response to certain drugs, and undergo necrotic cell death. Cisplatin reliably induces such acute tubular necrosis in murine systems. The role of DCs in cisplatin nephrotoxicity has recently been addressed using CD11c-DTR mice that express the diphtheria toxin receptor in CD11c$^+$ cells (Jung *et al.* 2002). Injection of diphtheria toxin into these mice permits conditional (albeit systemic) ablation of CD11c$^+$ DCs. However, CD11c is expressed at lower levels also by activated CTL and NK cells, as well as by distinct macrophages like those in alveoli or in the splenic marginal zone (Probst *et al.* 2005), which are depleted to some extent as well. By contrast, plasmacytoid DCs express only low CD11c levels and are not targeted in these mice (Sapoznikov *et al.* 2007). Despite these restrictions, CD11c-DTR mice permit conclusions on the *in vivo* role of DCs with reasonable accuracy (Bar-On & Jung 2010). Using these animals, it has recently been shown that kDC depletion aggravates renal injury in cisplatin nephrotoxicity (Tadagavadi & Reeves 2010). Local inflammatory effects by dying DCs within the kidney were excluded by mixed bone-marrow chimeras. The underlying molecular mechanisms have not been clarified, but may relate to increased expression of inducible costimulatory ligand (ICOS-L) on DCs, which can suppress T cells (Akbari *et al.* 2002). These findings point towards an anti-inflammatory role of kDCs in cisplatin nephrotoxicity.

Kidney DCs in chronic renal disease

Systemic DCs in Lupus nephritis

Lupus nephritis is a serious complication of systemic lupus erythematosus (SLE), which occurs in the majority of lupus patients at some point (Foster 2007). It is initiated by glomerular deposition of immune complexes, followed by complement activation and production of pro-inflammatory cytokines and chemokines, which leads to renal inflammation. The immune complexes often contain auto-antibodies against self nucleoproteins, likely derived from dying cells. Numerous animal models with lupus-like symptoms are being used, including MRL/lpr, NZB/W F1, NZM2328, and B6/TC mice. These mice carry allelic variants or mutations in genes relevant in the immune system, which render them susceptible for autoimmune diseases (Foster 2007). Alternatively, injection of hydrocarbon oil induces a lupus nephritis-like disease, which is useful when knockout mice are required. Whilst much attention has been focussed at the roles of T and B lymphocytes, those of DCs have only recently been addressed. Observations in patients (Fiore *et al.* 2008) and in murine models indicate both systemic roles, in the induction of autoantibodies, and local roles, in intrarenal inflammation that compromises organ function.

Production of auto-antibodies against nuclear self antigens requires activation of autoreactive Th cells that stimulate B cells, a systemic event that occurs in lymphatic organs like the spleen. Since DCs phagocytose apoptotic and necrotic cells and are able to present self antigens (Albert *et al.* 1998; Inaba *et al.* 1998), they are likely to be the APC population that breaks Th cell-tolerance to self antigens in SLE. Increased numbers of DCs in thymus and spleen have been suggested to play a role in breaking central and peripheral immune tolerance respectively (Ishikawa *et al.* 2001). In aged BWF1 mice that develop lupus nephritis, thymic and splenic DCs produced high levels of the chemokine BLC (CXCL13) that attracts B cells (Ishikawa *et al.* 2001). Additionally, Georgiev *et al.* showed that injection of syngeneic bone marrow-derived DCs, which had been exposed to necrotic or apoptotic cells, induced high levels of IgG1 autoantibodies in wild-type C57/BL6 mice, whereas injection of macrophages did not, indicating that DCs and not macrophages can break self tolerance (Georgiev *et al.* 2005).

Immunogens in SLE are most probably derived from dying cells. Apoptosis and thus provision of immunogens for autoantibody production in lupus is triggered by type I interferons, which are mainly produced by plasmacytoid DCs. Type I interferon production can be stimulated by circulating chromatin-containing immune complexes from lupus patients (Baechler *et al.* 2004). Furthermore, type I interferon in the serum of lupus patients can convert circulating monocytes into DCs that present autoantigens (Blanco *et al.* 2001). These observations support the notion that DC subsets are differentially involved in lupus pathogenesis.

A pro-inflammatory role of DCs in lupus pathogenesis was further supported by studies in B6.TC mice, which produce antinuclear nephritogenic auto-antibodies and develop glomerulonephritis. In these mice, DCs accumulated in lymphoid organs due to greater production in the bone marrow and to reduced apoptosis. Additionally, DCs showed reduced expression of co-stimulatory molecules and inhibited the function of regulatory T cells (Tregs) by production

of high levels of IL-6 (Wan *et al.* 2007), suggesting that abnormal DC maturation might contribute to disease progression.

A hint at protective roles of DCs came from studies in SIGIRR-deficient mice. This is an immunosuppressive mediator expressed by DCs and macrophages. Mice that lacked SIGIRR showed aggravated hydrocarbon oil-induced lupus (Lech *et al.* 2008, 2010). These findings demonstrate that DCs not only break tolerance in SLE, but also mediate certain immuno-suppressive functions in lupus pathogenesis. It is possible that the suppressive functions are lost in manifest lupus nephritis.

Kidney DCs in lupus nephritis

Lupus nephritis to date is the only condition in which DCs have been found to infiltrate glomeruli (Bagavant *et al.* 2006; Tucci *et al.* 2008). The Th1–driving cytokine, IL-12, is produced by macrophages and DCs within glomeruli in this condition, illustrating their ability to provide a pro-inflammatory microenvironment (Tucci *et al.* 2009). In the tubulointerstitium, kDC numbers in nephritic BWF1 mice were increased and production of BLC was noted. Co-stimulatory blockade together with cyclophosphamide reduced the number of renal $CD11c^+$ and in turn reduced B and Th cell infiltration and nephritis (Ishikawa *et al.* 2001; Schiffer *et al.* 2003), suggesting that kDCs attract effector immunocytes into the kidney. Additionally, in MRL-Fas(lpr) mice, DCs secreted the pro-inflammatory mediator high mobility group box protein (HMGB-1) via p38 mitogen-activated protein kinase (MAPK) activation. Inhibition of p38 MAPK decreased numbers of $CD11c^+$ cells in the kidney and in the spleen, reduced HMGB-1 protein in the kidney and improved kidney pathology (Iwata *et al.* 2009), identifying a potential therapeutic approach. In NZM2328 mice, progression of acute lupus nephritis towards chronic glomerulonephritis was accompanied by T cell activation and expansion in the renal lymph nodes (Bagavant *et al.* 2006). The authors did not rule out the possibility that T cells might also be stimulated by DCs inside the kidney. Taken together, these findings support the notion that kidney-resident DCs might promote renal infiltration by effector immunocytes, i.e. T cells, B cells or macrophages and thereby contribute to the progression to renal failure (Bagavant & Fu 2009). Further studies to directly address the role of kDCs in models of this important nephritis form are necessary.

Kidney DCs in other glomerulonephritis models

DCs have been histologically detected in periglomerular infiltrates in human glomerulonephritis and in various murine models thereof (Janssen *et al.* 1998; Kruger *et al.* 2004; Fujinaka *et al.* 2007; Woltman *et al.* 2007; Segerer *et al.* 2008; Tucci *et al.* 2009). Nephrotoxic nephritis (NTN) is a model for human crescentic glomerulonephritis, which is characterized by rapidly progressive glomerular damage and crescentic cellular infiltrates. It is induced by injection of a nephrotoxic antiserum, generated in sheep by vaccination with murine kidney cortex (Assmann *et al.* 1985; Lang *et al.* 2005; Tipping & Holdsworth 2006). Upon injection, sheep antibodies are taken up by DCs in lymphatic organs, and are used to activate specific Th1 cells and B cells. Due to their specificity, the antibodies bind to cortical antigens within the kidney. This allows local DCs and macrophages to capture and present them to infiltrating Th1 cells, which leads to an inflammatory response of the DTH type, with macrophages as the main effector cells (Tipping & Holdsworth 2006; Kurts *et al.* 2007).

We previously used CD11c-DTR mice to show that early depletion of DCs in NTN (days 4 and 10 after disease induction) aggravated renal damage, indicating a protective role of kDCs (Scholz *et al.* 2008). kDCs from nephritic mice stimulated T cell proliferation more potently than those from healthy mice and induced IL-10 and IFN-γ expression in Th cells. IL-10 is known to attenuate NTN whereas conflicting results have been reported for the role of IFN-γ (Tipping *et al.* 1997; Kitching *et al.* 1999; Ring *et al.* 1999; Timoshanko *et al.* 2002). The induction of IL-10 may have been mediated by ICOS-L expressed by kDCs in nephritic mice. Blockade of ICOS-L has been shown to aggravate NTN (Odobasic *et al.* 2006), reminiscent of the aggravation after early DC ablation (Scholz *et al.* 2008). A similar protective role for DCs involving up-regulation of ICOS-L-expression has recently been shown for cisplatin induced nephropathy, a model for acute kidney injury discussed above (Tadagavadi & Reeves 2010). Naturally occurring T_{regs} are known to attenuate NTN, by suppressing effector T cells in lymphatic organs (Wolf *et al.* 2005). Also here, a role of DCs in induction of such T_{regs} is likely, but has not been formally shown.

Contrasting these findings, we have recently shown a pro-inflammatory role for renal DCs in a model of T cell-mediated glomerular injury. In that study, we used transgenic NOH mice that express the model antigens ovalbumin and hen egg lysozyme in glomerular podocytes (Heymann *et al.* 2009). Co-injection of antigen-specific $CD8^+$ and $CD4^+$ T cells into these mice resulted in periglomerular mononuclear infiltrates and inflammation of parietal epithelial cells, resembling the histological picture in rapid-progressive glomerulonephritis in humans. DCs played two roles in the NOH model: First, they cross-presented glomerular antigen in the renal lymph node and activated CTL, which in turn infiltrated the kidney and released more glomerular antigen. Second, DCs in the kidney presented these antigens to Th cells, which resulted in intrarenal cytokine and chemokine production and in recruitment of macrophages, monocyte-derived DCs and more CTL. Depletion of DCs in nephritic mice by employing the CD11c-DTR transgenic system disbanded the periglomerular infiltrates, indicating that kidney DCs were required for its maintenance (Heymann *et al.* 2009). Hence, kidney DCs can link glomerular injury and tubulointerstitial infiltration, which is important since spreading of glomerular injury to the tubulointerstitium critically determines kidney function (Bohle *et al.* 1996).

Open questions for future studies

Recent studies revealed that kDCs are centrally involved in various models of kidney disease, including some that are not primarily immune-mediated (Table 2, Figure 1). This is not surprising given their key roles in diseases affecting for example the intestinal tract, the lung or the skin. However, recent data are conflicting, and at present it is completely unclear why kDCs were protective in some renal disease models and pro-inflammatory in others. One possible explanation is that the methods currently used to ablate DCs in mice are not completely specific for DCs, let alone for those in the kidney (Probst *et al.* 2005; Bennett & Clausen 2007; Kitamoto *et al.* 2009). Thus, some effects attributed to kDCs, which have been extrapolated from experiments that used such techniques, may in fact be due to functions of DCs in tissues other than the kidney, or even to non-DCs, such as macrophages that are targeted by Clo-Lip and to some extent also in CD11c-DTR mice (Probst *et al.* 2005; Bennett & Clausen 2007; Kitamoto *et al.* 2009). An alternative explanation may come from considering the DC maturation state. As described above, kDCs possess a tolerizing phenotype under steady-state-conditions, which seems reasonable since kDCs constantly encounter foreign antigen and would cause permanent inflammation if they were pro-inflammatory. Persistent inflammatory conditions, for example in chronic glomerulonephritis, might mature the kDCs, which thereby become immunogenic.

There are numerous models of renal disease in which the role of kDCs has not been studied sufficiently or not at all, for example experimental autoimmune glomerulonephritis (EAG), a murine model for anti-GBM nephritis, or rat models of nephritis. The lack of suitable antibodies specific for rat DC subsets, and the unavailability of transgenic rats that allow conditional depletion of DCs have thus far precluded addressing their role in these animals. This is regrettable, because many relevant models for human nephritis exist only in rats, such as Adriamycin-, Heymann- and Thy1-nephritis. But at least the Clo-Lip depletion technique (Van Rooijen & Sanders 1994) should be applicable.

The expression of the macrophage marker F4/80 by most of the renal $CD11c^+$ MHC II^+ DCs implies that there must be considerable overlap between kDCs and previously described renal macrophage subsets (Lin *et al.* 2009), but the exact extent of this overlap is unknown. At present there is an ongoing debate about when a mononuclear phagocyte may be classified as a macrophage or a DC (Steinman & I-doyaga 2010). Extreme points of view have been taken (Hume 2008) and contradicted (Heath & Carbone 2009). This controversy appears somewhat semantic, given that both the DC and the macrophage field have been developing for a long time, albeit more or less separate from each other. A mononuclear phagocyte may well fulfill the current criteria of both DC and macrophage. These terms may merely represent differentiation extremes in a function continuum of mononuclear phagocytes and drawing a clear demarcation in mutual consent between scientists of the DC and macrophage fields will be difficult. And even if possible, it is unclear whether this would help understanding kidney function or disease. Assessing functional abilities, such as the capacity to activate T cells, to phagocytose or to produce antibacterial effector molecules, appears a more purposeful approach to APC classification (Kruger *et al.* 2004). This should be kept in mind before embarking on extensive studies aimed at subdividing kDCs or macrophages into numerous subsets solely defined by their expression of surrogate

Table 2 Functions of DCs in animal models

Model	DC function	Citation
Steady state		
Healthy mice	Surveillance of the tubulointerstitium	Soos *et al.* (2006)
Healthy mice	T cell tolerance against innocuous small-molecular weight antigens	Lukacs-Kornek *et al.* (2008)
Acute renal injury		
Ischaemia/reperfusion injury	Production of pro-inflammatory cytokines, attenuation of damage after Clo-Lip, increased T cell stimulation in renal LN	Dong *et al.* (2005, 2007)
Unilateral ureter obstruction (UUO)	Stronger induction of Th17 cells; attenuation of damage after Clo-Lip	Dong *et al.* (2008), Kitamoto *et al.* (2009)
Cisplatin nephrotoxicity	Aggravation of kidney damage after depletion in CD11c-DTR mice	Tadagavadi and Reeves (2010)
Chronic renal disease		
Lupus nephritis	Systemic promotion of autoantibody generation; Suppression of such responses by SIGIRR; intrarenal attraction of autoreactive T and B cells by chemokines; expansion of autoreactive T cells in the renal lymph node	Ishikawa *et al.* (2001), Bagavant *et al.* (2006). Lech *et al.* (2008, 2010)
Nephrotoxic Nephritis (NTN) (model of crescentic glomerulonephritis)	Aggravation of kidney damage after early depletion using CD11c-DTR mice	Scholz *et al.* (2008)
T cell-mediated glomerular injury (NOH model)	Intrarenal stimulation of Th1 cells; attenuation of kidney damage after depletion using CD11c-DTR mice	Heymann *et al.* (2009)

markers like CD11c, F4/80, Gr-1, Mac-1 or DC-SIGN, whose functional roles are unclear. In the DC field, several overlapping nomenclatures for subsets currently exist and one commonly used underlies Table 1 (Shortman & Naik 2007). However, general consensus on a DC subset classification has yet to be reached (Steinman & Idoyaga 2010).

Of supreme importance is the clarification of the role of kDCs in human nephritis. Determining DC subset markers, and perhaps even more so, of activation markers, may open new opportunities for immunohistological analysis of renal disease. First steps towards this aim have been made by histological studies examining kidney sections of nephritic patients (Woltman *et al.* 2007; Fiore *et al.* 2008; Segerer *et al.* 2008; Tucci *et al.* 2009). Antibodies specific for the various subsets of human DCs have recently become available, eg. BDCA-1, -2 or -3, or DC-SIGN (Autissier *et al.* 2010). However, these markers are not expressed by murine DCs, so that knowledge gained in animal experiments may not easily be translated to human DCs. Nevertheless, a systematic appraisal of DC numbers, their tissue distribution pattern, subtype and, most importantly, their functional state may shed new light on the involvement of DCs in kidney disease and open new diagnostic opportunities. Finally, the development of drugs that suppress pro-inflammatory DC responses may permit novel therapeutic avenues in kidney disease.

Acknowledgements

We apologize to all colleagues whose work could not be cited due to space restrictions. The authors are supported by the German Research foundation (DFG grants Ku1063/5 and Ku1063/6, Sonderforschungsbereiche 704 and 645, Transregio 57, Klinische Forschergruppe 228), the German Academic Exchange service (DAAD) and the German National Academic Foundation (Studienstiftung des deutschen Volkes).

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