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Dendritic cells in progressive renal disease: some answers, many questions

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FULL REVIEW

ABSTRACT

Renal disease results from a variety of insults, but whatever its genesis, ongoing inflammation will drive progressive fibrotic disease. Dendritic cells link innate and adaptive immunity by presenting antigens, but they act also in an antigen-independent manner. While systemic dendritic cells (DCs) establish nephritogenic adaptive immunity, DCs are also present in the kidney. The tubulointerstitium is endowed with a network of mononuclear phagocytes, many having dendritic cell characteristics. While the roles of renal DCs are complex, recent evidence demonstrates that in adaptive immune responses affecting the kidney, DCs in the cortical interstitium express the chemokine receptor CX3CR1, are CX3CR1 dependent and are important in ongoing antigen recognition by effector CD4+ T cells, leading to progressive disease. Medullary DCs do not share this potent antigen-presenting function and CX3CR1 dependence. Though macrophages have a pathogenic role in antigen-independent renal fibrosis, whether interstitial DCs have any role is not clear. The participation of local and systemic DCs in progressive renal disease varies according to their involvement as antigen-presenting or local innate cells, the nature of the pathogenic process, and the involvement of the glomerulus, the cortical tubulointerstitium and the medulla in disease.

Keywords: chemokine, dendritic cells, glomerulonephritis, macrophage, renal fibrosis

INTRODUCTION

Renal disease is caused by a diverse range of insults, the kidney being affected by multiple immune, inflammatory and metabolic insults, but in progressive disease leading to end-stage kidney disease, interstitial fibrosis and glomerulosclerosis is almost universal. In many cases, fibrotic injury results from ongoing inflammation, with frustrated attempts at healing resulting in dysregulated and persistent matrix deposition. Thus, sclerosis and atrophy represent failed attempts at resolution, thwarted by the presence of persisting inflammatory and metabolic derangement. The genesis of this inflammation is not hard to conceptualize in antigen-driven forms of renal disease. The kidney can be targeted by virtue of it expressing autoantigens, by antigens being lodged in the kidneys or by antibody-induced disease leading to complement and leukocyte-mediated injury. However, even in diseases that in the past have been viewed as haemodynamic or metabolic in origin, inflammation plays a role in progressive injury. In the kidney, cells central to this process are mononuclear phagocytes, consisting of monocyte/macrophages and dendritic cells (DCs).

DCs are present in most tissues and lymphoid organs in the body, including the kidney. In health, they form a sentinel network to sense and report infectious threats, both to activate adaptive immunity and to allow antigen-specific effectors to localize to sites of inflammation. Immature 'unlicensed' DCs help maintain tolerance by anergizing autoreactive T cells. While DCs have the capacity to secrete pro- and anti-inflammatory cytokines as innate cells, their key specialized function is as professional antigen-presenting cells (APCs). DCs that have been activated by the presence of inflammatory signals induce immunity by migrating to (and by residing in) secondary lymphoid organs. These T helper cells direct adaptive immunity, both humoral and cellular. After the induction of active T cell immunity, local APCs present antigens to specific effector T cells at peripheral sites. In protective immunity, these locally active T cells mediate pathogen control and clearance, but in pathological inflammation and autoimmunity, they contribute to local tissue injury. Similar events occur in recurrent exposure to the antigen, when effector memory T cells recognize an antigen in the periphery presented by APCs to induce delayed-type hypersensitivity-like responses and recruit and activate other inflammatory cells.

There are a number of subtypes of DCs, the details of which have been recently reviewed [1]. DCs reside in peripheral tissues, with the capacity to migrate to secondary lymphoid organs, or they exist within lymph nodes, spleen and other

lymphoid tissue. DCs also exist in the thymus, where they are important in thymic T cell selection, but this aspect of DC function will not be considered further in this review. Although the nomenclature and classification of DCs has been and is complex, the current concepts are that there are two broad types of DCs, plasmacytoid DCs and classical DCs [1]. Plasmacytoid DCs function differently from other DC types, in that they are functionally specialized to sense foreign or altered nucleic acids and produce Type I interferons as well as presenting antigens. Classical DCs reside in secondary lymphoid organs and in peripheral tissues. Different tissues possess DCs with different functions, best suited to their role within that particular organ [1, 2]. During inflammation, blood-borne mononuclear phagocytes are recruited. These cells may arise from monocyte-like precursors and could differentiate into several cell types with a variety of functions [2], including antigen presentation to effector T cells. The cells are known as inflammatory DCs [1, 3]. The murine DC system has been studied more extensively, due to its capacity for genetic alteration, experimental studies and access to tissues. While some markers differ, similar DC types exist between mouse and human. This detailed classification of murine and human DCs has been reviewed recently [1].

This review focuses on the potential role of DCs in progressive renal disease in native kidneys. It will not directly refer to renal transplantation, where although many of the principles may be the same, additional complexities exist, including the presence of donor and recipient DCs, indirect and direct presentation, and altered lymphatic drainage from the graft. Assessing the role of DCs in kidney disease is complicated by the plasticity of DC and monocyte/macrophages and in some instances it is difficult to definitively (or least simply) separate one from another. The overlap between renal macrophages and DCs, collectively termed renal mononuclear phagocytes was reviewed in detail in 2012 [2]. Some of the important points highlighted in this key review [2] included the overlap in cell surface markers, origin and function between the two lineages, and the potential for plasticity. In the normal murine kidney, CD11b+ and F4/80+ cells have often been considered as macrophages, while CD11c+ cells have been classified as DCs. However, most CD11c+ cells in the kidneys are F4/80+ and many are CD11b+. CD11c+ cells derived from the normal mouse kidney collectively exhibit DC-like functions, but in the resting state are not as effective at inducing T cell responses as conventional splenic DCs [4, 5]. One approach to functional classification has been to consider DCs as directors of adaptive immune cells, and macrophages as immune effectors, while recognizing the overlap and plasticity of renal mononuclear phagocytes [6]. Table 1 provides an overview of progressive renal diseases that might be affected by DCs.

Table 1. Diseases in which systemic or local DCs could participate in progressive renal disease

1. Induction and perpetuation of nephritogenic immunity
A. *Systemically induced immunity to nephritogenic antigens*
Relevance to human disease: many diseases, including infection-related nephritis, lupus nephritis and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis.
Modelled by: most models of glomerulonephritis induced by active immunity, including autologous phase accelerated and non-accelerated 'anti-GBM' nephritis, active models of anti-MPO disease, experimental lupus nephritis.
B. *Locally induced immunity*
Relevance to human disease: possibly some forms of tubulointerstitial nephritis (without glomerular disease), Goodpasture's disease (anti-GBM glomerulonephritis) and primary membranous glomerulonephritis (anti-PLA2R) among others.
Modelled by: transfer of T cells specific for ovalbumin into NOH mice (expressing ovalbumin on podocytes) or RIPmOVA mice (expressing ovalbumin in the proximal tubules), potentially by GBM-specific CD4+ cell transfer (clones/cell lines) into naïve mice.
2. Local recognition of antigen-specific CD4+ cells
A. *Glomerular disease*
Relevance to human disease: forms of rapidly progressive glomerulonephritis with evidence of effector T-cell participation: anti-GBM disease, Class III/IV lupus nephritis, ANCA-associated vasculitis.
Modelled by: endogenous antigens: transfer of α3(IV)NC1 specific CD4+ cells. Planted antigen models: heterologous globulins (i.e. autologous phase 'anti-GBM' glomerulonephritis), model foreign antigens (e.g. ovalbumin), myeloperoxidase in the cellular component of anti-MPO disease
B. *Interstitial disease*
Relevance to human disease: tubulointerstitial nephritis (without glomerular disease), potentially the interstitial component of some glomerular diseases.
Modelled by: anti-tubular basement membrane disease, the interstitial component of autologous phase 'anti-GBM' nephritis.
3. T cell-independent effects of DCs
Relevance to human disease: potentially many other causes of progressive tubulointerstitial renal disease, including the tubulointerstitial component of diabetic nephropathy, obstructive nephropathy and hypertensive renal disease.
Modelled by: unilateral ureteric ligation, chronic injury post ischaemia reperfusion, chronic hypertensive models, renal mass reduction models.

RENAL DCS: THEIR ROLE IN STEADY STATE AND IN INFLAMMATION

Within the kidney, DCs reside mainly within the interstitium. Since their first description by Hart and Fabre [7], a number of studies have highlighted their presence and demonstrated their function as APCs [4, 5, 8–10]. Two studies, employing multiphoton confocal microscopy in fluorescent reporter mice, one using CX3CR1-GFP mice [8], the other using CD11c-EYFP mice [5], demonstrated the presence of cells with DC-like morphology and probing behaviours within the cortical tubulointerstitium *in vivo*. Further recent studies on the renal mononuclear phagocyte lineages have highlighted the overlap between surface markers, function and origin. Kawakami *et al.* [11] recently described five distinct mononuclear phagocyte populations within the normal mouse kidney based on their relative expression of CD11b and CD11c, with some types being able to stimulate naïve T cells. Fate map tracing using the DC lineage-specific marker Clec9A showed that in the murine kidney some of the cells that were previously considered renal macrophages are derived from DC precursors [12].

DCs are relatively abundant in the tubulointerstitial compartment in health and disease [4, 5, 7, 8, 13–16] and in some diseases, in local germinal centre-like structures [17]. In humans, as in mice, different subsets are present expressing

Table 2. Selected cytokines produced by DCs and their function in renal disease

Cytokine	Effects on T cell polarity	Inflammatory	Direct effects on fibrosis	Role in experimental renal disease
IL-12	Th1	Pro- (indirect)	?	Th1 inducing [36]
IL-1β	Th17	Pro-	Pro-fibrotic [37]	Several mechanisms [38, 39]
IL-23	Th17	Pro-	?	Th17 maintaining [40, 41]
IL-10	Suppressive	Anti- (usually)	Anti-fibrotic [42]	Protective [43]
Type I interferons		Pro-	? Promotes FSGS [44]	Promoting systemic autoimmunity [45]
TNF		Pro-	Pro-fibrotic [46]	Several mechanisms [47]
TGF-β	Tregs; Th17 (with IL-6 and IL-1β)	Anti-	Pro-fibrotic [48]	Pro-fibrotic [48] acutely protective [49]
IL-6	Th17	Pro-	? No direct role [50]	Systemic pro-inflammatory [51] Protective acutely [52]

FSGS, focal segmental glomerulosclerosis; Th1, T helper cell 1; Th17, T helper cell 17.

different surface markers. However, the majority of studies show that DCs, though present, are not common in glomeruli [13, 14, 18]. In steady state, DCs are only rarely found in glomeruli [18]. In inflammation, while numbers increased, they remain relatively uncommon [13, 18]. Differences in the presence or number of DCs between glomerular and interstitial compartments complicate our attempts to understand the role of renal DCs in disease. Although we know that effector CD4+ T cells recognize antigens within glomeruli, induce injury and influence innate effector cells within glomeruli [19–21], and that DCs are instrumental in the generation of effector CD4+ cells in lymphoid organs, we are not sure yet whether local DCs are required for the localization and effector function of antigen-specific CD4+ cells within glomeruli. Studies using bone marrow chimeric mice and mice with lineage-specific MHC II deficiency suggest that antigen recognition and T-cell activation leading to severe glomerular injury can occur via MHC II on intrinsic glomerular cells [22, 23], including podocytes [24], but other leukocytes (for example DCs, monocytes, B cells or even neutrophils) within glomeruli could also be important. However, not all studies show a paucity of DCs in glomeruli. Two human studies suggest significant glomerular DC accumulation in disease: one found a significant number of both classical and plasmacytoid DCs in the glomeruli of patients with proliferative lupus nephritis [25], the other, in anti-neutrophil cytoplasmic antibody (ANCA)-associated glomerulonephritis found DCs in glomeruli, but to a lesser extent [16]. Experimentally, one group defined a CD8+ DC that infiltrated glomeruli in autoimmune anti-glomerular basement membrane (GBM) glomerulonephritis in rats to induce effector T cell apoptosis [26]. In addition to the discordance on studies of DC number in glomeruli, *in vivo* studies in mice show that leukocytes, present constitutively in normal glomeruli, migrate a considerable distance bidirectionally within the glomerular capillary loops [21]. These recent findings suggest that even if uncommonly present, DCs (or other leukocytes) within glomeruli might be able to survey large areas of glomerular capillaries.

There is evidence that renal DCs, and DCs in the renal draining lymph node help maintain tolerance in a steady state by capturing low-molecular weight-filtered antigens and peptides [27, 28]. Unlicensed interstitial renal DCs that express low levels of positive costimulatory molecules and do not secrete pro-inflammatory cytokines sample filtered peptides or peptides derived from small filtered proteins [27]. Constitutive migration of these immature DCs to draining lymph nodes is likely to help maintain tolerance to self-antigens. Further support for 'resting' renal DCs being anti-inflammatory comes from observations of the lower capacity of these cells to stimulate naïve T cells [5], that some populations produce IL-10 and can generate foxp3+ inducible regulatory T cells (iTregs) *ex vivo* [11], and that depletion in experimental acute kidney injury [29], or early in the autologous phase of experimental 'anti-GBM' glomerulonephritis, worsens tubulointerstitial injury [30], potentially via IL-10.

In the presence of innate inflammation, renal CD11c+ cells become active, express co-stimulatory molecules and migrate from the kidney. They become more effective at presenting soluble and membrane-bound antigens and activating naïve CD4+ and CD8+ cells draining lymph *in vivo* [5, 9, 31, 32]. As well as being more effective at presenting antigen to naïve CD4+ T cells, renal DCs can quickly produce inflammatory cytokines, for example, TNF in ischaemia reperfusion injury [33]. There are however, brakes on T cell activation: PD-1 ligands on DCs limit T-cell activation [9], neutrophil-derived MPO regulates DC function [34] and in humans *ex vivo*, activated primary proximal tubular cells also limit the activation of autologous DCs [35]. Table 2 summarizes some of the cytokines produced by DCs and their possible roles in renal disease.

HOW COULD DCS PROMOTE PROGRESSIVE RENAL DISEASE AND FIBROSIS?

Defining the contribution of DCs to progressive renal disease is complicated by several key issues, discussed above, including the dual roles of DCs in influencing adaptive immunity, as well as acting as innate cytokine-secreting cells. Progression in some diseases is heavily dependent on ongoing adaptive immunity, where the role of DCs is in perpetuating adaptive immunity that directs inflammation. In other conditions, for example, diabetic nephropathy, polycystic kidney disease and obstructive uropathy, adaptive immunity is unlikely to play a role, but innate inflammation is important. Therefore any function for DCs in these conditions is more likely that they act directly as pro- (or even anti-) fibrotic innate immune cells.

Some of the potential roles of DCs in renal disease are summarized in Figure 1, including reference to CX3CR1, discussed below. In influencing renal disease, DCs can act locally or systemically. There is also evidence, detailed below, that within the kidney, DCs may have different primary functions within different compartments of the kidney, specifically within the cortical interstitium and the medulla.

Systemic roles as APCs

DCs in secondary lymphoid organs are important in the induction and maintenance of systemic immunity. An increasing proportion of forms of glomerulonephritis are recognized as resulting from immunity to systemic antigens. Often, as for example, in systemic lupus erythematosus and ANCA-associated vasculitis, the antigens are autoantigens, but in infection-related forms of glomerulonephritis the primary immune responses are systemic and directed against a foreign antigen. Therefore, DCs that drain sites of antigen encounter systemically play a key role in these responses in chronic inflammatory states resulting in progressive renal disease, with the caveat that in established humoral autoimmunity, antigen-specific B cells may act themselves as potent APCs [53]. Events in the renal draining lymph nodes may be relevant for responses against renal tissue restricted antigens and after immune complex deposition [54–56].

Local roles as APCs

Adaptive immunity initiated by DCs generates antibodies that bind to peripheral targets as effectors, independent of local DCs. However, local DCs do play this APC role in presenting the antigen to CD4+ T cells in the cortical interstitium. Antigen-specific effector CD4 + T cell responses, requiring local MHC II expressing APC are now recognized as relevant to a number of forms of glomerulonephritis. DCs mediate this recognition in the cortical interstitium, though their role in the glomerulus is less clear, as discussed above. Experimentally, we know that CD4+ T cells recognize planted and endogenous antigens in glomeruli. Multiple studies using different antigens, including using transfer of T-cell lines and clones demonstrate that effector T cells mediated glomerular injury in an antigen-specific manner [19, 20, 56–59], but it is not yet clear which

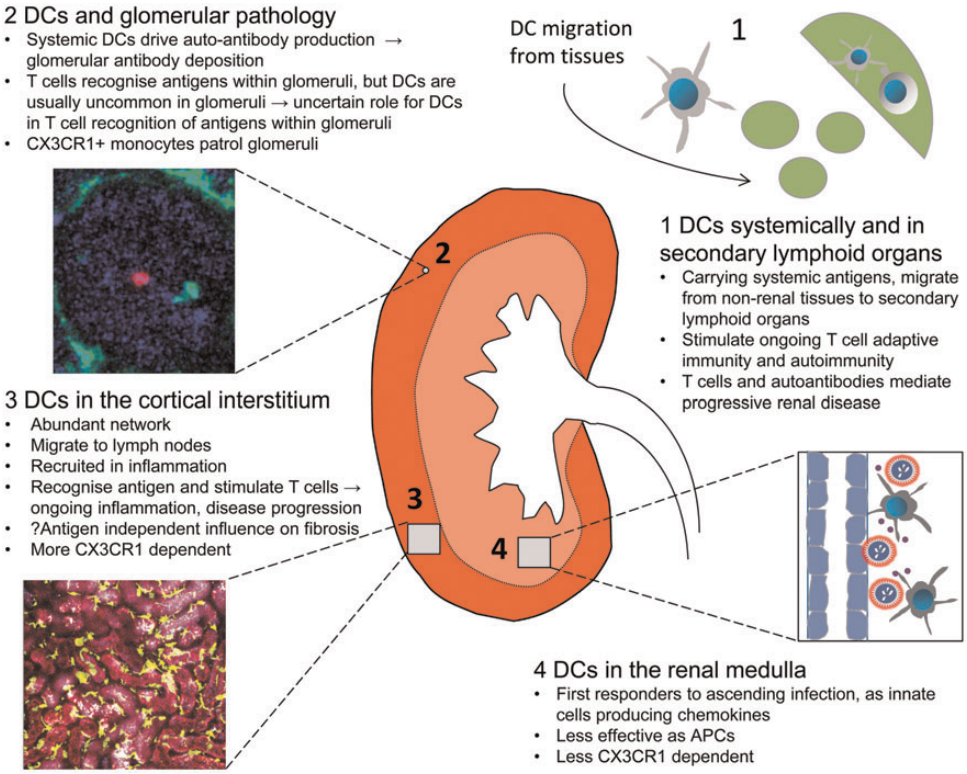

FIGURE 1: The potential roles of dendritic cells (DCs) in progressive renal disease, by location and compartment. (1) Most antigens in renal disease are systemic, so adaptive immune responses are stimulated on an ongoing basis by systemic antigens and DCs from other tissues and within secondary lymphoid organs (spleen and lymph nodes, green cartoon, top right). (2) DCs contribute to ongoing glomerular pathology by directing systemic cellular and humoral immunity, but the role of DCs in the recognition of antigen in glomeruli is unclear. CX3CR1+ monocytes patrol the glomerulus intravascularly. (3) The cortical interstitium is richly endowed with DCs that normally help to maintain tolerance to self-antigens, but in inflammation become potent stimulators of antigen-specific effector CD4+ cells and are dependent on CX3CR1. A direct pro-fibrotic role of DCs has not yet been defined. (4) In the renal medulla, DCs respond innately and rapidly to infection, producing chemokines (purple dots, cartoon, bottom right) that recruit neutrophils (red rimmed cells) in an early response to bacteria within the kidney. Medullary DCs are not CX3CR1 dependent. Illustrative photomicrographs are stills from *in vivo* multiphoton microscopy studies: (2) Glomerulus (Westhorpe C.A., Kitching A.R., Hickey M.J., unpublished image). Glomerular capillaries, blue, antigen-specific CD4+ cell red, CX3CR1+ cells green (within glomerular capillary loop and periglomerular). (3) Normal cortical interstitium (Snelgrove *et al.* [5], unpublished image from work published). Yellow cells are CD11c+ cells with dendritic morphology, epithelial cells are labelled in red via a cell tracker dye.

cell type(s) mediate this antigen-specific recognition within glomeruli.

Local roles as pro-inflammatory and pro-fibrotic innate cells

As well as their specialized antigen-presenting roles, DCs secrete a variety of cytokines that help protect from infectious agents. These cytokines can be pro- or anti-inflammatory, some could have direct pro-fibrotic effects (Table 2). While it is well known that many of these cytokines can contribute to renal disease, or dampen inflammation, it is less clear whether renal DC production of these cytokines makes a significant contribution.

CX3CR1 ON DCS: A MORE SPECIFIC THERAPEUTIC TARGET IN PROGRESSIVE RENAL DISEASE?

CX3CR1, renal cortical DCs and experimental glomerulonephritis

A recent paper from Christian Kurts' group in Bonn, Germany, sheds more light on the role of DCs in the progression of renal inflammation [60]. This group has made important contributions to understanding the biology of renal DCs over the last 10 years [4, 27, 28, 30, 56, 61]. The latest paper suggests that targeting CX3CR1 (the fractalkine receptor), a chemokine receptor expressed by DCs and monocytes, may offer more targeted therapy for progressive renal disease in the future. While chemokines are important in a number of areas of biology, they are perhaps best known for their capacity to recruit cells to tissues, particularly in inflammatory states. Fractalkine (CX3CL1) is somewhat unusual as a chemokine in that it is cell surface anchored [62] and has only one receptor, CX3CR1. CX3CL1 is present in human and experimental glomerular and interstitial renal disease [63–65]. It is expressed on endothelial cells and a variety of other cell types, including tubular epithelial cells and is induced by a variety of inflammatory stimuli [66–68]. Similarly, CX3CR1 has been detected in a variety of human renal diseases, present on CD3+ and CD68+ leukocytes in both the glomerulus and the interstitium [69], increased in fibrotic disease on fibroblasts [70] and in some reports, also DCs [70, 71].

Using a model of glomerulonephritis induced by injecting an anti-basement membrane antibody raised in sheep, which acts as a planted foreign antigen, Hochheiser *et al.* [60] examined the relationship between DC-derived CX3CR1 and disease. CX3CR1-deficient mice developed less severe glomerulonephritis than in other reports that inhibited or deleted CX3CR1 or its ligand CX3CL1 [72–74]. However, unlike some previously published papers, which focussed on impaired monocyte recruitment to glomeruli [72], Hochheiser *et al.* [60] found that interstitial DC influx into the kidney was mediated by CX3CR1, but DCs from other organs did not seem to be particularly CX3CR1 dependent. Recruitment of inflammatory DCs to the kidney was also mediated by CX3CR1. This is likely to be important in the progression of disease mediated by adaptive immunity, as renal DCs migrate to draining lymph nodes in inflammatory states, to be replaced by inflammatory renal mononuclear phagocytes. As well as potentially acting as macrophages, these recruited cells can differentiate into DCs, ensuring effector CD4+ antigen-specific T cells can recognize antigens locally within the tubulointerstitium.

Medullary DCs behave differently and are less CX3CR1 dependent

Hochheiser *et al.* address, at least to some degree, a key question in the future treatment of immune-mediated disease: how to target injurious inflammatory responses without undue and suppressive effects on host defence. The contention is that, at least in mice, CX3CR1 is an attractive therapeutic target, firstly because it is preferentially expressed in renal DCs (much less so in DCs within other organs) and secondly, because it is required for recruitment of inflammatory DCs. In addition, intriguing data were presented implying that renal host defence might be unimpaired by targeting DCs [60]. CX3CR1+ DCs are enriched in the renal cortical tubulointerstitium and are important in progressive renal disease mediated by adaptive immune responses. Therefore, could inhibiting the function of renal DCs render the host more susceptible to intrarenal infection? Pyelonephritis, the most important and common renal infection, typically results from ascending infection. In this context, DCs in the renal medulla seem to be first responders, with a lesser role for cortical DCs. Hochheiser *et al.* [60] show in experimental murine pyelonephritis that the host defence was unaffected in the absence of CX3CR1. The medullary DCs that are the initial responders to ascending infection are less CX3CR1-dependent and also have less important antigen-presenting functions.

While common forms of renal infection are usually mediated by ascending infection, with initial medullary involvement; some infections do involve the cortex. Another paper published shortly after the Hochheiser paper [75] showed that CX3CR1 in renal cortical DCs is important in host defence in murine systemic candidiasis involving the kidney. Interestingly, clearance from other organs was substantially less affected, supporting a more important role for CX3CR1 in the kidney compared with other organs. Renal cortical candida infection tends to occur more often in people with significant neutropaenia, and therefore may or may not be a significant issue in itself if inhibiting CX3CR1 was to be a strategy employed in humans.

Other CX3CR1-expressing cells: are they relevant to progressive kidney disease and host defence?

Besides DCs, other immune cells also express CX3CR1. There is evidence that these cells, and CX3CR1 expression on these cells, is important in renal disease—in addition to CX3CR1 on DCs [60], though it is uncertain how this might relate to progressive chronic renal disease. CX3CR1 is expressed on circulating and patrolling intravascular monocytes in healthy mice. These monocytes are constitutively present both in the glomerular capillaries [21] and in the interstitial circulation, sense danger and induce acute neutrophil mediated endothelial injury in peritubular capillaries [76]. These

CX3CR1+ monocytes could play roles in infection and inflammation in the kidney, or elsewhere in the body. In human lupus nephritis, CX3CL1 was present in glomeruli, with infiltrating monocytes expressing CX3CR1 [77]. Neutralizing CX3CR1 in non-accelerated 'anti-GBM' glomerulonephritis in rats improved glomerular histology, lessened proteinuria and diminished glomerular T cell and macrophage infiltration [73].

Within the interstitium, CX3CR1 mediates monocyte recruitment and promotes injury acutely in experimental ischaemia reperfusion injury [78, 79], which could be relevant chronically. In addition to monocytes, a proportion of human T cells also express CX3CR1 and *in vitro* these T cells can be attracted to proximal tubular cells [80]

These data make the concept targeting CX3CL1–CX3CR1 in progressive renal disease more attractive, as targeting CX3CR1, as well as minimizing T-cell mediated tubulointerstitial disease via DC inhibition, may also have other beneficial effects, including limiting glomerular leukocyte recruitment. However, if patrolling CX3CR1+ monocytes are important in the host defence elsewhere in the body, anti-CX3CR1 therapy might be less specific and have more systemic immunosuppressive effects.

Are DCs critical in all types of progressive renal disease?

The concept that in the future in renal disease, we can limit progressive disease by selectively affecting 'bad' or pathogenic renal DCs (those that promote pathological inflammation) while not impairing the function of 'good' renal DCs (those that would assist in protecting from ascending infection) is an attractive one. However, renal disease and its progression is complex, as discussed above. We now know that renal DCs are important in antigen-directed T-cell-mediated inflammation [60, 61], but do renal DCs have pro-fibrotic roles in the diverse range of renal diseases non-mediated by adaptive immunity?

DO RENAL DCS HAVE PRO-FIBROTIC ROLES INDEPENDENT OF THEIR ROLES IN ENHANCING ADAPTIVE IMMUNITY?

The active participation of DCs in ongoing T-cell-mediated inflammation means that healing and repair with mature and healthy matrix deposition, and restoration of function, is unlikely to occur. Therefore, if DCs are allowing effector T cells to recognize locally antigens on an ongoing basis (or systemically promoting ongoing adaptive immunity resulting increased antibody deposition or T-cell recruitment), then they are highly likely to be profibrotic. In these settings, the role of DCs in promoting immunity is clearly linked to promoting fibrosis. But do DCs promote fibrosis directly as pro-inflammatory innate cells independent of their roles in adaptive immunity? This is less clear—and finding the answers to this question complicated by DCs' close relationship and overlap with macrophages, the definition of what is a DC, as well as complexities in experimental depletion strategies throughout the renal mononuclear phagocyte systems [2, 81].

Observations in human renal fibrosis

Many human DC studies focus on inflammation and find that the more inflamed the kidney, the more DCs are present in the interstitium. As chronic inflammation leads to fibrosis, these findings clearly need to be taken into consideration. In studies focussed specifically on human renal fibrosis, renal DC numbers are increased, with increased expression of the co-stimulatory molecule CD86, suggesting increased activation, and increased classical DC (probably inflammatory DCs) production of TGF-β [82]. As might be anticipated, in renal fibrosis, CX3CR1 is upregulated on several cell types, including DCs [70].

Experimental studies in progressive renal injury not driven by innate immunity

Experimentally, most work on a potential role of DCs in 'innate' fibrosis uses the murine unilateral ureteric obstruction (UUO) model. There is as yet no absolute clarity in the evidence derived from this model, due at least in part to the complex and overlapping phenotypes of renal mononuclear phagocytes (DCs and monocyte/macrophages), as well as the different techniques used in depletion studies, each with their strengths and weaknesses [81], but there is little hard evidence that DCs themselves contribute innately to fibrosis. It is likely that that a macrophage (or macrophage-like) subset is directly pro-fibrotic and that DCs, although becoming more active, do not play a direct pro-fibrotic role [5, 83, 84]. *In vivo* multiphoton microscopy showed that CD11c+ cells with a dendritic morphology were more active morphologically, tended to cluster around damaged tubules, and showed a higher number of dendrites per cell [5]. The total number of DCs tended not to alter over the first 3 days, potentially due to migration to draining lymph nodes being balanced by an influx of monocyte-like cells then differentiating into $CD11c^{hi}$ inflammatory DCs, though another study found an early increase in DCs with increased early cytokine production [85]. Although the DCs were functionally activated (as they acquired a more potent capacity to stimulate antigen-specific T cells), using the CD11c-DTR system (CD11c+ cells are deleted by the administration of diphtheria toxin), fibrosis at Day 7 was not altered by CD11c+ cell depletion prior or during the process. Depletion at Day 7 did not alter fibrosis at 2 weeks. Therefore, unlike experimental autologous phase 'anti-GBM' glomerulonephritis [61], it appears that depleting DCs later in an innate inflammatory response does not diminish fibrotic disease.

CX3CR1's influence on experimental renal fibrosis has been examined in other settings. CX3CR1-deficient mice were protected in a hypertensive model [86] and in the context of chronic changes after ischaemia reperfusion injury [87]. In this setting the outer medulla was most affected, via diminished macrophage recruitment in the absence of CX3CR1. Whether this is due to CX3CR1's effect indirectly via DCs or directly via monocytes is not clear.

Clearly the classical antigen-presenting, antigen-specific T-cell-stimulating functions of DCs as APCs are important in the progression of renal disease mediated by adaptive immunity, but it is still unclear whether renal DCs have direct effects

on fibrosis mediated by innate immunity, inflammation and metabolic insults, which maybe more macrophage mediated. Interestingly, in chronic murine adriamycin nephrosis, a model of progressive renal disease, infusions of *ex vivo*-generated anti-inflammatory macrophages, or activated plasmacytoid DCs both reduce chronic inflammation and injury [88, 89].

Can we learn from studies in fibrosis in other organs?

The role of DCs in progressive disease in other tissues has been assessed, but as in the kidney, the situation is unclear. As in human renal disease, DCs accumulate in human fibrotic lung disease, [90]. Experimentally, in toxin-induced liver and lung fibrosis, DCs are more prominent and active [91, 92]. Functionally, in experimental liver disease DCs seem to be responsible for the early increased pro-inflammatory cytokines found [91]. One study found DCs to be pro-fibrogenic [93], but another showed that DCs accelerated regression of fibrosis in a carbon tetrachloride induced model [94]. Most recently a further series of studies in experimental fibrosis (induced by bile duct ligation) suggests that macrophages contribute to fibrosis but DCs do not [95], findings aligned with the emerging view from studies in UUO.

While fibrosis in different organs has a number of common features, we cannot assume that the mediators and mechanisms all are similar. Examples of these organ-specific differences that involve the kidney include the role of the plasminogen, which is protective in experimental pulmonary fibrosis [96], but unexpectedly (yet convincingly) pathogenic in UUO [97, 98], and the pathogenic role of platelet-derived growth factor-C in the kidney not being replicated in the liver [99].

SUMMARY AND FUTURE CHALLENGES

DCs are important cells in kidney health and disease. Understanding their roles in progressive disease is complex, relating to their plasticity and overlap with monocyte/macrophages, the systemic and local roles of DCs, their potentially divergent roles at different stages of disease and the recent recognition of compartment specific functions for DCs. In established inflammation, renal DCs within the cortical interstitium present antigen to activated effector T cells, augmenting and perpetuating inflammation that promotes progressive renal disease. In this setting, local roles for DCs as APCs within glomeruli remain uncertain. Some of the key questions regarding of DCs in progressive renal disease are outlined in Table 3.

In progressive renal disease that features innate inflammation, there is no clear role for DCs, though macrophages (some of which might display some DC-like features) are important. Immunotherapy for renal disease remains in most cases, relatively non-specific, but recent data suggest targeting CX3CL1–CX3CR1 could be a more selective and effective approach, though we still need to understand more about the off-target (non-DC) effects that could potentially be beneficial and/or deleterious. Lastly, studies that attempt to define the role of DCs and identify new therapeutic studies should ideally be performed in well-defined and understood model systems so that their relevance to humans can be clearly assessed.

Table 3. The role of DCs in progressive renal disease: current questions

1. Are renal DCs pro-fibrotic, independent of their effects as APCs. If so, are they best thought of as macrophages or DCs (and to what extent is this distinction important)?
2. Can we dissect out the relative roles of elements of the renal mononuclear phagocyte system (DCs and monocyte/macrophages) in progressive renal disease and target cells with a harmful phenotype?
3. Can we better isolate the systemic and local effects of DCs experimentally to understand their roles?
4. Antigens within glomeruli can be recognized by effector CD4+ cells, but given the paucity of DCs in glomeruli, are they important, and what other cells act as APCs?
5. To what degree are innate pro-fibrotic responses within the kidney 'generic' and how much are their direction and intensity determined by the underlying stimuli?
6. What effect does CX3CR1 inhibition have on cells other than renal cortical DCs and glomerular monocyte/macrophages. Are these effects beneficial, or could there be adverse effects?
7. Can we harness anti-inflammatory and tolerogenic effects of DCs locally and/or systemically to treat renal disease?

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CONFLICT OF INTEREST STATEMENT

None declared.

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