

**REVIEW ARTICLE**

# Renal Mononuclear Phagocytes in Lupus Nephritis

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Renal mononuclear phagocytes are a highly pleiotropic group of immune cells of myeloid origin that play multiple protective and pathogenic roles in tissue homeostasis, inflammation, repair, and fibrosis. Infiltration of kidneys with these cells is a hallmark of lupus nephritis and is associated with more severe disease and with increased risk of progression to end-stage renal disease. This review presents current knowledge of the diversity of these cells and their involvement in kidney inflammation and resolution and describes how they contribute to the chronic inflammation of lupus nephritis. A better understanding of the subset heterogeneity and diverse functions of mononuclear phagocytes in the lupus nephritis kidney should provide fertile ground for the development of new therapeutic approaches that promote the differentiation and survival of protective subsets while targeting pathogenic cell subsets that cause inflammation and fibrosis.

## Introduction

Lupus nephritis (LN) is a common manifestation of systemic lupus erythematosus that can cause irreversible renal injury. Although the prognosis of LN has improved substantially over the past 50 years, standard immunosuppressive therapies induce complete remission in less than 50% of treated patients. The rate of progression of LN to renal failure has plateaued in the United States in the past 20 years, and approximately equal to 10% of patients develop end-stage renal disease (ESRD) within 10 years of diagnosis. This failure reflects disease complexity and heterogeneity as well as insufficient patient access to high-quality medical care (1).

Although the pathologic classification of LN is based predominantly on renal glomerular inflammation, it is increasingly recognized that interstitial inflammation and fibrosis are associated with a worse long-term prognosis. The presence of renal macrophages, and dendritic cells (DCs) (mononuclear phagocytes) in particular, correlates with more severe disease and an increased likelihood of disease progression (2,3). There has therefore been increasing interest in understanding the diversity of these cells and how they contribute to tissue injury in LN as well as in multiple other inflammatory and fibrotic diseases.

This review will describe the heterogeneity of the mononuclear phagocyte system in tissues and how this landscape changes during inflammation and resolution. It will then show how

this general paradigm applies to LN and how this knowledge may inform approaches to treat LN and prevent progression to ESRD.

## Pathogenesis of LN

LN is initiated by the deposition of nucleic acid containing autoantibodies and debris in the glomeruli. Subendothelial deposits activate the glomerular endothelium and engage complement; this induces the recruitment of circulating proinflammatory cells, leading to proliferative disease and the formation of glomerular crescents. By contrast, subepithelial deposits face the urinary space and cause podocyte injury with foot process effacement, leading to proteinuria (4). Mesangial deposits in isolation are less likely to directly damage the glomerular filtration apparatus. In addition, soluble inflammatory mediators derived either from the circulation or from activated glomerular cells amplify glomerular cell activation and injury (5–10).

The glomerular filtration apparatus comprises the endothelial layer, the glomerular basement membrane, and the podocyte layer. Podocytes and glomerular endothelial cells secrete growth factors to support each other's survival, and mesangial cells provide growth factors that support the endothelium. Because of these interrelated functions, injury to any glomerular cell type can eventually damage the others (10–12). This is followed by glomerular cell dedifferentiation and loss of integrity of the whole

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glomerular tuft. Because glomerular cells have limited regenerative capacity (13,14), sequential insults to LN kidneys result in progressive glomerular loss. Compensatory glomerular hypertrophy and glomerular hypertension then compromise tubulointerstitial viability because interstitial capillaries are supplied solely by vascular runoff from the glomeruli. Disease progression is therefore associated with tubulointerstitial hypoxia and compromise of epithelial cell metabolic pathways, leading to cell death (15,16). Although renal epithelial cells have the capacity to regenerate, interstitial capillary rarefaction may be irreversible. Tissue damage and hypoxia leads to the accumulation of immune infiltrates in the interstitium; this is followed by the differentiation of multiple cell types, such as stromal cells and pericytes, into fibroblasts (1).

Changes to the renal tubulointerstitium (including tubular atrophy, fibrosis, and interstitial infiltrates) are known prognostic markers for progression to ESRD in patients with LN (17,18). Furthermore, immunohistochemical studies of kidney biopsies from patients with LN have suggested that the presence of renal macrophages, both glomerular and tubular, is associated with a worse prognosis in patients with LN, particularly at the second biopsy (2,19,20). The predictive power of the second biopsy reflects the ability of this biopsy to detect those patients in whom initial therapy has failed to control inflammatory lesions and in whom early fibrosis fails to reverse (2,18). Because mononuclear phagocytes can play a role in both inflammation and repair, newer studies are now beginning to address the heterogeneity and functions of these cells in renal injury in general, and in LN in particular,

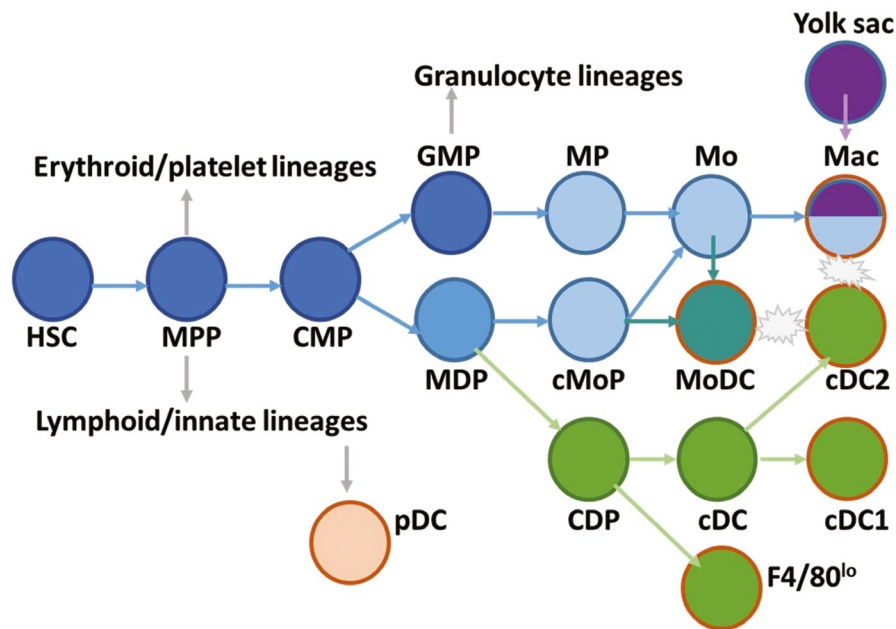
to address whether it is possible to target pathogenic populations while retaining those that could mediate repair.

## The origins and development of renal macrophages and DCs

Renal mononuclear phagocytes derive from precursors that form in the fetal yolk sac and from hematopoietic precursors in the bone marrow (Figure 1).

**Yolk sac-derived macrophages.** Yolk sac-derived macrophages are the source of resident macrophages in multiple organs, including the kidneys. Resident macrophages of embryonic origin are long lived and self-renewing, and they play an essential role in tissue homeostasis by monitoring the tissue for pathogens and removing any dead materials. These cells are slowly replaced throughout life by macrophages of hematopoietic origin that take on the organ-specific features of the resident cell. The rate of this replacement varies in each organ and increases during periods of tissue inflammation; if the organ is irradiated, the entire population can be replaced from bone marrow-derived cells that adopt a tissue-specific profile as they enter the tissue microenvironment (21,22).

**Bone marrow-derived macrophages and DCs.** Bone marrow-derived macrophages and DC are highly related subsets that derive from common progenitors. Monocytes are short-lived circulating cells that differentiate into either macrophages or



**Figure 1.** Development of the myeloid lineage from hematopoietic stem cells (HSC) or from yolk sac macrophages (Mac). Cells with an orange border are found in normal kidneys. The three cell types connected by grey clouds have similar phenotypes and may be difficult to distinguish in inflamed tissues by phenotyping alone. cDC, classic dendritic cells; CDP, common dendritic cell progenitors; CMoP, common monocyte progenitors; CMP, common myeloid progenitors; GMP, granulocyte macrophage progenitors; MDP, macrophage dendritic cell progenitors; Mo, monocyte; MoDC, monocyte-derived dendritic cells; MP, monocyte progenitors; MPP, multipotent progenitors; pDC, plasmacytoid dendritic cells.

DCs once they enter tissues. Macrophages are highly phagocytic cells that play both pathogenic and protective roles during tissue injury and repair. DCs engulf smaller-sized material than macrophages and are efficient antigen-presenting cells that function to activate the adaptive immune system. All these cells are highly pleiotropic, and recent studies have shown overlapping phenotypes and functions between the macrophages and DCs that infiltrate injured tissues (22).

**Renal mononuclear phagocytes.** Normal kidneys contain a network of long-lived tissue-resident macrophages that occupy niches around the periphery of glomeruli and adjacent to tubules and peritubular capillaries; these cells function in immune surveillance and homeostasis (23–26). Resident renal macrophages in mice are initially of yolk sac origin but are replaced by cells of hematopoietic origin as the mice become adults (27). These resident macrophages are characterized by the high expression of F4/80 and CD64 and are different from those in many other organs because there is no basement membrane that separates them from endothelial cells, allowing them to rapidly take up small immune complexes and other small particles in a manner analogous to that of splenic macrophages and Kupffer cells (25).

The normal kidney also contains smaller populations of other phagocytic cells. Renal DCs include both type 1 classic dendritic cells (cDC1) and type 2 classic dendritic cells (cDC2), which are phenotypically and functionally distinguishable subsets. cDC1 cross-present antigen to CD8 T cells via class I major histocompatibility complex and can also induce regulatory T cells. cDC2 are classic antigen-presenting cells that interact with and activate the adaptive immune system. Further subsetting of DCs has been reported, and even more phenotypes have been identified in the setting of inflammation (22,27). Under homeostatic conditions, some renal DCs migrate to lymph nodes, where they help to maintain tolerance to renal antigens. Studies in mice show that in contrast to resident macrophages, kidney cDCs turn over rapidly, suggesting that they traffic continuously into the kidneys (27,28). Plasmacytoid DCs are also present in normal kidneys. These cells derive from the lymphoid lineage and function to produce innate cytokines, including type I interferons (IFNs), on exposure to innate stimuli. Finally, there is a small renal population of cells of common DC progenitors origin that express CD11b but are low for F4/80. These cells have phenotypic differences from both macrophages and cDC2 (23,27).

The precise location of DC subsets in normal kidneys has not been fully mapped because of the lack of specificity of many myeloid cell markers. Extensive flow cytometry characterization using multiple markers and lineage tracing experiments in mice are beginning to address this issue (22,27). Using the cDC-specific *Zbtb46* as a reporter for all cDCs and *Snx22* as a reporter for cDC1, cDCs were found to be localized predominantly around blood vessels (29). Experiments using *Clec9a* as a reporter have by contrast suggested that up to 30% of renal

cells with a resident macrophage phenotype (F4/80<sup>hi</sup>/CD64<sup>hi</sup>) and localization are cDCs (27). The interpretation of the fate mapping studies depends on the specificity of the reporters for the various cell lineages, and further studies are needed to fully understand the role of each subset during homeostasis and disease.

Single-cell RNA sequencing analyses of immune cells from normal mouse kidneys have recently been reported (30). Single-cell analysis samples the most abundantly expressed genes in individual cells at a single time point and therefore represents only a snapshot of the overall diversity of renal mononuclear phagocytes. Nevertheless, these studies have confirmed the presence of the subsets described above and are beginning to allow for further subsetting and functional analysis of renal macrophages and DCs, especially in diseased tissues.

### General alterations of renal mononuclear phagocyte function in inflammatory renal diseases

**Macrophages.** Macrophages are highly pleiotropic cells that can rapidly be polarized *in vitro* to multiple phenotypes and alter their phenotype and function *in vivo* in response to their microenvironment. During acute kidney injury in mouse models, proinflammatory macrophages are recruited to the glomeruli under the influence of chemokines and other chemoattractants. Both classical monocytes (CD14<sup>+</sup> in humans and Ly6C<sup>hi</sup> in mice) and nonclassical monocytes (CD16<sup>+</sup> in humans and Ly6C<sup>lo</sup> in mice) can acquire an inflammatory phenotype in tissues and contribute to tissue injury. TLR7 engagement, in particular, is associated with the recruitment of nonclassical (patrolling) monocytes to activated endothelium (31). Proinflammatory function of infiltrating macrophages is reinforced by inflammatory cytokines and other damage associated molecular patterns by tubular release of micro-RNAs and by activation of inflammasome-mediated pathways (32). These cells produce inflammatory cytokines, nitric oxide synthase, procoagulants, and matrix metalloproteinases, and their pathogenic role has been confirmed in mouse models in which their depletion during the inflammatory phase after acute injury attenuates renal injury (26,33).

As renal disease transitions from the acute to the chronic phase, both infiltrating and resident renal macrophages take on an alternatively activated reparative phenotype (34,35). This could be due to a switch in cell phenotype or sequential recruitment and differentiation of different cell populations. Alternatively activated macrophages play a major role in removal of debris and collagen, regulation of inflammation, and regeneration of the tubular epithelium; their depletion during the repair phase of injury exacerbates renal fibrosis (33,36). Induction of this phenotype is regulated by local cytokines and metabolic conditions. In mice, transfer of macrophages polarized by interleukin 4, interleukin 13, and/or interleukin 10 promotes renal repair after acute injury. Conditions in local microenvironment, such as tissue hypoxia and

iron metabolism and tubular secretion of colony-stimulating factor 1, can also drive alternative macrophage polarization. Nevertheless, excessive accumulation of reparative macrophages results in the production of profibrotic mediators, such as transforming growth factor  $\beta$  and platelet-derived growth factor.

Studies in several human renal diseases have shown an association between alternatively activated macrophages in renal biopsies and poorer disease outcome and fibrosis. Similarly, macrophages with an alternatively activated phenotype can promote both glomerulosclerosis and interstitial fibrosis in rodent models of chronic renal injury (26). The balance between renal repair and chronic fibrosis is regulated by cross talk between fibroblast precursors, tubular epithelium, and macrophages (37,38).

The full scope of pathogenic and protective populations of macrophages in chronically inflamed kidneys and the specific roles infiltrating and resident macrophages (39,40) are still not completely delineated. Macrophages with the capacity to digest and remove collagen *in vitro* have been identified (41), but the precise molecular and functional characteristics of these cells and how to induce them *in vivo* remain to be established. Matrix metalloproteinase 13 has emerged as a key matrix metalloproteinase that promotes resolution of fibrosis in multiple organs, including the kidney (42,43). Phagocytic receptors of the TAM family may also regulate resolving functions; for example, MerTK-positive macrophages promote resolution of inflammation, whereas MerTK-negative macrophage subsets induce the differentiation of inflammatory fibroblasts (40,44). By contrast, the phagocytic TAM receptor Axl promotes tissue fibrosis by enhancing TLR signaling and metabolic reprogramming (45). Recent studies have highlighted the role of the neural guidance protein Netrin-1 as an antiinflammatory mediator that is induced in macrophages in hypoxic areas of tissue (46). Netrin-1 stimulates the production of pro-resolving lipid mediators, shortens the time required for resolution of inflammation, and promotes tissue regeneration. However, Netrin-1 macrophages can also promote fibrosis during chronic inflammation. Interestingly, the interaction of Netrin-1 with its receptor induces adrenergic nerve remodeling and release of norepinephrine, which promotes fibrogenesis (47).

Recent discoveries with respect to the regulation of immune cell function by intracellular metabolic pathways have enhanced our understanding of the mechanisms for macrophage polarization. Inflammatory macrophages are characterized by an increase in glycolysis and a decrease in mitochondrial function with production of succinate and itaconate as a result of breaks in the Krebs cycle (48). Succinate enhances production of inflammatory cytokines and reactive oxygen species. By contrast, itaconate has both an antibacterial and an antiinflammatory role, acting to restore homeostasis. Alternatively activated and pro-resolving macrophages are characterized by an increase in fatty acid oxidation and mitochondrial respiration and by the secretion of arginases that produce metabolites that suppress inflammatory responses (49). An emerging interest has been to define transcription factors

that dictate programs that regulate the metabolism, phenotype, and function of macrophage subsets (21). Resident and infiltrating macrophages are regulated by different transcription factors, and macrophage programs can also be influenced by the type of material they phagocytose in each specific niche. For example, Spi-C transcription factor regulates a macrophage program needed for iron handling, whereas Nr1h3 is induced by the accumulation of cellular cholesterol (via uptake of lipids from dying cells) and, in turn, can suppress inflammation, promote macrophage survival, and enhance antiinflammatory apoptotic cell clearance (13,50,51). Notably less is known about myeloid cell subsets and states and the core transcription factors that regulate them in the kidneys than in other major organs.

**DCs.** During inflammatory disease, infiltrating DCs derive from both monocytes and circulating DCs. Like macrophages, DCs in tissue are heterogeneous and can perform both inflammatory and suppressive functions. Distinction of tissue macrophages from tissue DCs can be difficult, especially in inflammatory settings in which infiltrating cells display features of both cell types (22,52). This has resulted in some confusion over nomenclature of renal myeloid cells that is still not fully resolved. Studies in mouse models of renal inflammation suggest that cDC1 are protective, whereas cDC2 are pathogenic (22). Mouse splenic cDC2 have recently been divided into two subsets that express different transcription factors and appear to employ different metabolic programs (53). Gene expression differences between these two subsets suggest that cDC2A are more likely to be involved in tissue repair, whereas cDC2B are more likely to be proinflammatory. Other subsets include CCR7 expressing DCs that have the capacity to migrate to lymph nodes and may also help to organize local lymphoid infiltrates. Transcription factors that direct DC ontogeny and function are beginning to be described (53). How each of the DC subsets contributes to renal injury and repair is currently not known.

## Alterations of the renal myeloid compartment in LN

The renal mononuclear phagocyte compartment undergoes extensive remodeling as LN evolves, with an influx of new myeloid cells, the accumulation of mixed immune infiltrates, and changes in the function of resident cells.

**Glomeruli.** Glomerular macrophages can be abundant in LN, with heterogeneity among mouse models and patients with LN. These cells are located either within the glomerular tuft, where they are adherent to glomerular capillary walls, or within the glomerular crescents (54). Phenotypic studies in mice have shown that there are at least two subpopulations of these cells in glomeruli. In mouse models characterized by overexpression of TLR7, glomerular macrophages are located within glomerular capillaries



and are F4/80<sup>lo</sup>, CD11c<sup>hi</sup>, and Ly6C<sup>lo</sup>, characteristic of nonclassical or patrolling macrophages. These cells express the transcription factor Nr4a1, and deletion of this transcription factor abolishes their recruitment to glomeruli and attenuates glomerular injury (55). In the NZM2328 model, infiltrating F4/80<sup>lo</sup>, CD11b<sup>+</sup>, CD11c<sup>-</sup> cells are found in the glomeruli of severely proteinuric mice; these cells are also Ly6C<sup>lo</sup> and have an alternatively activated phenotype (6,56). The molecular characteristics of macrophages located in glomerular crescents have not yet been reported in mice.

In human LN, glomerular macrophages correlate with the severity of glomerular lesions, being found more frequently in diffuse proliferative disease. Studies using a limited number of cell surface markers suggest that these cells are heterogeneous and may include both inflammatory and reparative phenotypes (20).

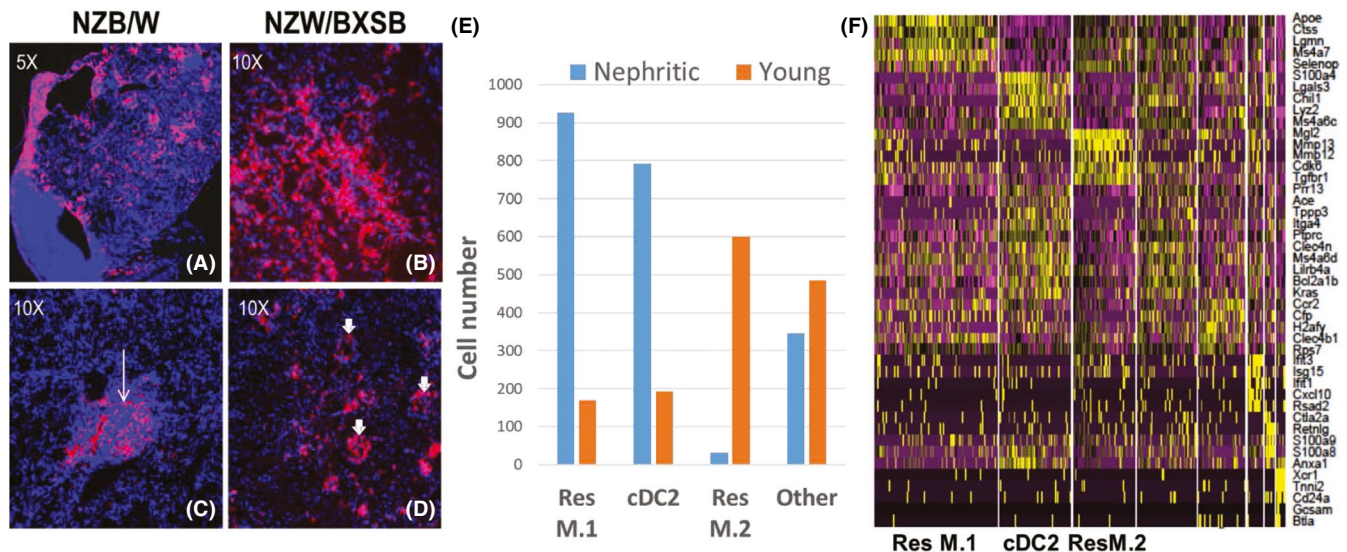
**Interstitial resident cells.** Macrophages with a resident phenotype increase in number during LN. Peritubular renal macrophages are susceptible to immune complex-mediated activation because of their anatomic location near small peritubular vessels without an intervening basement membrane (25). Our phenotypic and single-cell studies in mice have confirmed that there is a major shift in the resident macrophage profile during LN, with loss of protective and homeostatic functions and acquisition of an alternatively activated/reparative phenotype (23,57). An analogous population of macrophages with an

alternatively activated profile is highly represented in human LN biopsies (58).

**Immune cell infiltrates.** Mixed tubulointerstitial leukocyte infiltrates, sometimes with features of lymphoid organization, are found in LN (2,17,18,59) and are associated with renal scarring and a worse prognosis. These infiltrates contain both cDC1 and cDC2, especially during advanced disease (3). In human LN biopsies, CD209 expressing cDC2 are found in periglomerular regions, within lymphoid infiltrates, and scattered in the interstitium (60). CD103 (cDC1) DCs and plasmacytoid DCs are also present in smaller numbers both in mice and humans with LN (3,23). Approximately 40% of patients who have moderate to severe infiltrates progress to ESRD over a 4-year period (17), but it is still not known how to distinguish those patients who will progress from those who will not.

### Lessons learned from molecular profiling and single-cell analyses of LN kidneys

Our early studies in diverse mouse models of LN identified a myeloid cell signature that was shared among LN mouse models and human biopsies. Using flow cytometric analyses, we found both expansion and activation of the dominant CD11b<sup>+</sup>/F4/80<sup>hi</sup> renal macrophage population during active LN as well as a large population of cDC2 during proliferative systemic lupus



**Figure 2.** Diversity of mononuclear phagocytes in LN kidneys. **A**, F4/80 staining of macrophages in a kidney from a nephritic NZB/W mouse shows localization around glomeruli and in the interstitium but exclusion from lymphoid aggregates. **B**, F4/80 staining of macrophages in a kidney from a nephritic NZW/BXSB (TLR7 overexpressing) mouse shows localization around glomeruli and extensive infiltration in the interstitium. **C**, CD11c staining of classic dendritic cells (cDCs) in a kidney from a nephritic NZB/W mouse shows localization within the mixed perivascular immune infiltrate. **D**, CD11c staining in a kidney from a nephritic NZW/BXSB (TLR7 overexpressing) mouse shows localization inside glomerular tufts; these cells are most likely nonclassical (patrolling) monocytes. **E**, Single-cell RNA sequencing (RNASeq) analysis of CD11b/c cells from nephritic and prenephritic (young) mice. Bars show the number of cells in the three major clusters. Resident macrophages are in resident macrophage cluster 2 (Res M.2) in young mice and predominantly in resident macrophage cluster 1 (Res M.1) in nephritic mice. Also note the expansion of the cDC2 population in nephritic mice. **F**, RNASeq analysis of CD11b/c cells from NZB/W mice shows eight subclusters of cells. The top five genes for each cluster are shown on the right.

erythematosus nephritis that disappears during remission. We found an additional population of CD11c-positive glomerular cells in mice overexpressing TLR7 (23,61) (Figure 2).

Single-cell analyses are now beginning to reveal the complexity of the myeloid cell landscape in LN kidneys. Our studies in NZB/W mice have identified at least eight subsets of renal mononuclear phagocytes, with significant differences in the relative representation of each subset between prenephritic and nephritic mice (62) (Figure 2). We found that the three major clusters of cells in NZB/W mice are two clusters of resident macrophages and a cluster of cDC2. Resident macrophages from nephritic and prenephritic mice cluster separately because of the differences in gene expression that occur in this subset at disease onset. We also identified smaller populations of cDC1, CCR7<sup>hi</sup> DCs, monocyte-derived DCs, proliferating cells, and cells expressing an inflammatory and IFN signature. Interestingly, an additional population was found in Sle1.Yaa mice corresponding to the glomerular subset of CD11c<sup>+</sup> cells (62).

Our team is part of the Accelerating Medicines Partnership–Systemic Lupus Erythematosus (AMP-SLE), which is addressing the complexity of LN using single-cell RNA sequencing (scRNASeq) analysis of renal cells (58,63). Recently, the AMP-SLE group has successfully completed scRNASeq analysis of a total of 160 LN biopsies using 10x Genomics technology. This AMP-SLE phase 2 study will yield a rich set of data that can be correlated with disease outcome in a manner that has previously been unprecedented. Initial scRNASeq data of CD45<sup>+</sup> immune cells isolated from the first 23 biopsies analyzed in the AMP-SLE phase 1 study have been published and include 466 myeloid cells (58). Although this sample size is rather small, we were able to identify five subpopulations of cells, of which only one was detected in normal kidneys harvested from healthy living renal donors. We found four subpopulations of macrophages cluster myeloid (CM0, CM1, CM2, and CM4), of which only CM0 was detected in the peripheral blood. Three of these populations, CM0, CM1, and CM4, are related along a developmental trajectory, starting with tumor necrosis factor–producing CD16<sup>+</sup> nonclassical monocytes (CM0) that transition to a phagocytic (CM1) and then to an alternative macrophage phenotype (CM4) that also produces inflammatory chemokines. We classified the fourth population that was found in both healthy donors and LN biopsies (CM2) as resident macrophages. These cells acquired both an IFN signature and an antiinflammatory signature in LN biopsies (58). We also detected a small population of cDC2, but their number was too small to analyze them in detail. The results of the phase 2 study will be available later this year; these data include a much larger population of myeloid cells, and preliminary analyses indicate that additional myeloid cell subsets are present (A. Arazi: personal communication). Our preliminary analyses also indicate that there are substantial similarities between the populations that are present in humans and those we find in mice (64), suggesting that mechanistic studies will be possible in selected mouse models.

It is impractical to collect sequential human renal biopsies for testing causal disease mechanisms or monitoring treatment responses. It is therefore of great interest to test whether myeloid cell subsets appear in the urine and can be used as surrogate markers for renal infiltration. Preliminary analyses of the AMP-SLE phase 1 samples have shown that myeloid cells constitute the majority of immune cells in the urine, especially CM1 cells (58), suggesting that these have access to the urinary space, most likely as a result of localization in glomerular crescents. Further analyses in the AMP-SLE phase 2 observational study will address whether the inflammatory myeloid cell subsets correlate with renal infiltrates and/or responses to treatment and whether urine can be used to assess treatment responses and prognosis. Ongoing mapping studies will also determine the location of the various myeloid cell subsets.

## Applications to clinical care

Many types of mononuclear phagocytes are found in the kidneys of individuals with LN. A better understanding how each infiltrating cell type contributes to renal injury is now needed so that pathogenic cells can be targeted, whereas those involved in organ protection and repair can be spared. Because the features of reparative macrophages that promote resolution and resorption of collagen and extracellular matrix components are not well defined and may be organ specific (35,65–67), it is not always possible to extrapolate studies from other inflammatory diseases and organs to LN.

There are several approaches to identifying the function of tissue-derived myeloid cell subsets. Recent studies of synovial macrophages found that the presence of MerTK<sup>+</sup> synovial tissue macrophages during disease remission was associated with protection from disease flare after cessation of treatment (44). When isolated, these cells failed to induce inflammatory fibroblasts in coculture experiments. By contrast, MerTK<sup>−</sup> macrophages were more likely to produce inflammatory mediators and interact with stromal cells to induce the development of inflammatory fibroblasts that promote fibrosis. An alternative approach that can be used in the case of organs, like kidneys, that are difficult to access, is to compare the phenotype of organ-specific macrophages with that of macrophages induced by a broad panel of cytokines and to reproduce a similar phenotype *in vitro* that can then be used for coculture studies (68). Finally, mouse models can be particularly useful for functional and therapeutic studies if they reflect human physiology. In this context, comparison of data from mouse models with the AMP-SLE phase 2 data will be highly informative.

## Conclusions

Identifying and targeting pathogenic myeloid cell subsets and prevention and treatment of renal fibrosis should improve the

treatment of LN. Therapeutic manipulation of metabolic pathways offers some new opportunities for the treatment of inflammatory diseases, including LN (69). Strategies are beginning to emerge for modulating macrophage glycolysis through the inhibition of inducing signals, such as toll like receptors and the NLRP3 inflammasome (32). Induction of reparative macrophages will require a better understanding of how fibrosis and resolution are balanced, but new inroads are being made by using mouse models of injury and repair. For example, the combination of a decoy form of soluble Axl with an antagonist of MerTK shedding was highly effective at promoting repair in a model of cardiac injury (45). Another novel approach is the use of  $\alpha 1$  agonism to oppose the activity of Netrin-1; this strategy prevented fibrosis in a mouse model of early interstitial pulmonary fibrosis, although it was ineffective at reversing established fibrosis (47). Therapies can also be directed at correcting metabolic abnormalities of the tubular epithelium because these cells induce profibrotic functions in adjacent macrophages (15,70). Prevention of recruitment and/or differentiation of inflammatory macrophages and DCs is another potential approach. In this context, it is of interest that B cell activating factor has a role in directing myeloid cell function that could help account for the therapeutic efficacy of belimumab in LN (71–73). Uncovering the role of each renal mononuclear phagocyte subset in LN should provide a fruitful area for research and further therapeutic discovery.

## AUTHOR CONTRIBUTIONS

Dr. Davidson drafted the article, revised it critically for important intellectual content, and approved the final version to be published.

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