

## The Renal Mononuclear Phagocytic System

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### ABSTRACT

The renal mononuclear phagocytic system, conventionally composed of macrophages (M $\phi$ ) and dendritic cells (DCs), plays a central role in health and disease of the kidney. Overlapping definitions of renal DCs and M $\phi$ , stemming from historically separate research tracks and the lack of experimental tools to specifically study the roles of these cells *in vivo*, have generated confusion and controversy, however, regarding their immunologic function in the kidney. This brief review provides an appraisal of the current state of knowledge of the renal mononuclear phagocytic system interpreted from the perspective of immunologic function. Physical characteristics, ontogeny, and known functions of the main subsets of renal mononuclear phagocytes as they relate to homeostasis, surveillance against injury and infection, and immune-mediated inflammatory injury and repair within the kidney are described. Gaps and inconsistencies in current knowledge are used to create a roadmap of key questions to be answered in future research.

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The mononuclear phagocytic system in nonlymphoid organs such as the kidney is composed of diverse subsets of bone marrow–derived macrophages (M $\phi$ ) and dendritic cells (DCs).<sup>1</sup> M $\phi$  are defined as tissue-resident phagocytic cells that contribute to steady-state tissue homeostasis by clearing apoptotic material and producing growth factors. During infection, they perform antimicrobial effector functions such as phagocytosis and production of toxic metabolites and proinflammatory cytokines.<sup>1,2</sup> DCs, however, are defined primarily by the specialized functions of antigen presentation and regulation of immune effector cells. Classically, DCs collect antigenic material in tissues and then migrate to lymph nodes for the purpose of presenting antigen to naïve T cells.<sup>1,3</sup> As summarized in Table 1, however, M $\phi$  and DCs within the kidney exhibit

additional and at times, overlapping functional properties that extend beyond these classic paradigms. Furthermore, similar to mononuclear phagocytes in skin, lung, and gut, the predominant, resident renal mononuclear phagocytes (rMoPh) simultaneously express markers traditionally associated with either M $\phi$  or DCs.<sup>4–7</sup> Indeed, as discussed below, many research groups have characterized these rMoPh for over three decades as either M $\phi$  or DCs, despite growing evidence of phenotypic and functional overlap, creating a barrier to cohesive progress in the field.

Knowledge of rMoPh began with groundbreaking studies in normal kidneys of mice and rats that identified abundant dendritiform cells within the renal interstitium. These cells were designated antigen-presenting DCs on the basis of MHC class II expression<sup>8,9</sup> or

resident M $\phi$  because of F4/80 expression.<sup>8–10</sup> In addition, rare MHC class II<sup>+</sup> globular M $\phi$  were identified in the glomerulus<sup>11,12</sup> and subcapsular and periarterial connective tissue.<sup>13,14</sup> Subsequently, however, multicolor flow cytometry revealed substantial overlap and heterogeneity in expression of historically defined M $\phi$  (CD11b, F4/80, and CD68) and DC (CD11c, MHC II, and CD80/86) markers by interstitial rMoPh.<sup>15–19</sup> Along with similar descriptions in normal human kidney,<sup>20–22</sup> these studies established the predominant rMoPh at steady state as networked, dendritiform, interstitial cells that coexpress multiple markers previously thought to segregate M $\phi$  from DCs. Hence, many investigators, whether originating from M $\phi$  or DC disciplines, were unknowingly studying the same predominant rMoPh, while often neglecting knowledge from the other discipline. As a result, the use of markers as surrogates for M $\phi$  or DC functions within the renal mononuclear phagocytic system (Table 1) is increasingly questioned.<sup>22</sup> This debate has also been heightened by lack of specificity of reagents commonly used to induce loss of function of DCs or M $\phi$  (Table 2).

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**Table 1. Distinct and shared functions of macrophages and dendritic cells in the kidney**

|  |
|--|
| M $\phi$   |
| classic functions  |
| phagocytosis of tissue debris and pathogens  |
| mediation of tissue injury and disease progression   |
| activated phenotypes exhibit distinct polarized functions <sup>a</sup>   |
| contemporary additions   |
| phagocytosis to remodel matrix   |
| support for nephrogenesis and cell fate decisions  |
| paracrine role in angiogenesis and epithelial regeneration   |
| polarized function can be fibrogenic   |
| potent source of chemokines and cytokines <sup>a</sup>   |
| mediate anti-inflammatory/immunosuppressive effects through innate responses <sup>a</sup>  |
| DCs  |
| classic functions  |
| phagocytosis of antigen in kidney  |
| migration to renal lymph nodes   |
| antigen presentation to T lymphocytes  |
| contemporary additions   |
| antigen presentation within the kidney to restimulate or modify infiltrating T lymphocytes   |
| mediate anti-inflammatory/immunosuppressive effects through innate responses and modulation of T lymphocytes (peripheral tolerance) <sup>a</sup> |
| activated phenotypes exhibit distinct polarized functions <sup>a</sup>   |
| potent source of chemokines and cytokines <sup>a</sup>   |

<sup>a</sup>Overlapping functions.

This ambiguity resulting from conventional nomenclature, now recognized and intensely debated for the mononuclear phagocytic system in general,<sup>5</sup> dictates that functional properties are required to properly characterize the renal mononuclear phagocytic system.<sup>1</sup> Studies on whether the predominant interstitial rMoPh isolated from kidneys perform like splenic DCs by presenting antigen and activating naïve T lymphocytes or like peritoneal M $\phi$  by killing phagocytosed microbes showed the former function.<sup>15</sup> This finding supports other reports suggesting migratory and phagocytic properties more typical of DCs.<sup>16,23</sup> However, these early studies could not anticipate the multitude of additional M $\phi$  and DC functions now assigned to the renal mononuclear phagocytic system<sup>24–30</sup> or the fact that functional plasticity—rather than dichotomy—might exist depending on cues provided to rMoPh from the environment.<sup>22,29,30</sup> Moreover, the renal mononuclear phagocytic system at steady state changes dramatically during inflammation, in which resident and recruited rMoPh exhibit great heterogeneity and dynamic

phenotypes.<sup>30–32</sup> In light of these shifting paradigms, we reappraise here the current knowledge of the renal mononuclear phagocytic system. We focus on identifying gaps and inconsistencies in our understanding of the ontogeny and function of rMoPh in surveillance, tolerance, and tissue cytoprotection during steady state, as well as immunity, tissue injury, and repair associated with inflammation. The emerging role for plasticity within the renal mononuclear phagocytic system is also discussed. Notably, knowledge of these topics has come primarily by studying the mouse as a model organism, and translation to humans, which has been limited,<sup>20,21</sup> remains an important goal.

### ONTOGENY OF MONONUCLEAR PHAGOCYTES OF THE KIDNEY IN STEADY STATE

During the past 10 years, studies of specific transgene reporter mice and multicolor flow cytometry of mouse kidney cell preparations reveal many characteristics of resident rMoPh during normal health.

Transgene reporters of *cx3cr1* (CX<sub>3</sub>CR1) and *csflr* (CD115) fate map over 90% of rMoPh within the kidney at steady state.<sup>17,18,33</sup> The large majority of CX<sub>3</sub>CR1<sup>+</sup> cells is dendritiform rMoPh, which form a contiguous network throughout the entire renal interstitium of mice, lining the microvascular, peritubular, and periglomerular spaces.<sup>17,33,34</sup> These predominant rMoPh are definable by a marker profile: CD11b<sup>+</sup>MHCII<sup>+</sup>CX<sub>3</sub>CR1<sup>+</sup>CD11c<sup>+/-</sup>F4/80<sup>+/-</sup>CD103<sup>-</sup> (Figure 1, CD11b<sup>+</sup> rMoPh), which is similar to that of interstitial CD11b-like DC and tissue macrophages described in other nonlymphoid tissues.<sup>6,7,16–18</sup> Among this CD11b<sup>+</sup> rMoPh subset, the reported frequency of expression of CD11c (either with or without F4/80 coexpression) has varied between 40% and 90%,<sup>15–17,35</sup> indicating that additional phenotypic characterization of these cells is yet required. In addition, F4/80 is reportedly expressed preferentially by medullary rMoPh at steady state.<sup>10,17</sup>

The second definable rMoPh subset, representing  $\leq 5\%$  of steady-state interstitial rMoPh, exhibits the surface phenotype CD11b<sup>-</sup>MHCII<sup>+</sup>CX<sub>3</sub>CR1<sup>-</sup>CD11c<sup>+</sup>F4/80<sup>-</sup>CD103<sup>+</sup> (Figure 1, CD103<sup>+</sup> rMoPh) and is, therefore, not visible in CX<sub>3</sub>CR1-GFP reporter mice.<sup>18</sup> The function of this second subset in the kidney is unknown at present, but similar cells exist in skin, lung, and intestine where they perform specialized functions, including cross-presentation and induction of regulatory T cells.<sup>1,4,6,18,36</sup> Plasmacytoid DCs, which differ ontogenically, functionally, and phenotypically from CD11b<sup>+</sup> rMoPh and CD103<sup>+</sup> rMoPh, are difficult to detect in normal mouse and human kidneys and may be absent.<sup>20,21</sup> CD11b<sup>+</sup> rMoPh within normal glomeruli are scarce, more globular-shaped, and seem to lack CD11c and F4/80.<sup>15,19,37</sup> The rMoPh of normal human kidneys show generally similar anatomic distribution and population heterogeneity,<sup>20,21</sup> but not all murine markers (F4/80 and CX<sub>3</sub>CR1) can be used to classify human rMoPh. To the extent that it has been characterized to date, the phenotype of the predominant human rMoPh displays

**Table 2. Features and pitfalls of commonly used strategies to induce loss of function of rMoPh**

|  |
|--|
| CD11c-diphtheria toxin receptor mouse <sup>102</sup>   |
| conventional use   |
| ablation of CD11c <sup>+</sup> rMoPh <i>in vivo</i> to study loss of DC function within the kidney (Table 1)   |
| degree of fidelity   |
| CD11c is expressed by DCs systemically, not just within the kidney   |
| CD11c is expressed by the majority of CD11b <sup>+</sup> rMoPh, which may also perform functions associated with Mø  |
| CD11c is expressed by other cells such as activated T lymphocytes, alveolar Mø, and splenic marginal zone Mø   |
| pitfalls   |
| experimental outcomes are confounded by loss of function of other cells that express CD11c, both within and outside the kidney, including rMoPh that may function as Mø (Table 1); as a result, DC-dependent and -independent functions of rMoPh may not be separable, and products from rapid death of CD11c <sup>+</sup> cells may also influence immune responses |
| CD11b-diphtheria toxin receptor mouse <sup>103</sup>   |
| conventional use   |
| ablation of CD11b <sup>+</sup> rMoPh <i>in vivo</i> to study loss of Mø function within the kidney (Table 1)   |
| degree of fidelity   |
| CD11b is expressed by Mø systemically, not just within the kidney  |
| CD11b is expressed by the majority of CD11c <sup>+</sup> rMoPh, which may also perform functions associated with DCs   |
| CD11b is expressed by other cells such as monocytes, B lymphocytes, and granulocytes   |
| pitfalls   |
| experimental outcomes are confounded by the loss of other cells that express CD11b, both within and outside the kidney, including rMoPh that may function as DCs (Table 1); as a result, Mø-dependent and -independent functions of rMoPh may not be separable, and products from rapid death of CD11b <sup>+</sup> cells may also influence inflammatory responses  |
| Clodronate liposomes <sup>104</sup>  |
| conventional use   |
| ablation of phagocytic rMoPh, often to study loss of phagocytic function within the kidney   |
| degree of fidelity   |
| all mononuclear phagocytic cells are ablated systemically  |
| rMoPh are broadly phagocytic   |
| does not discriminate between phagocytic rMoPh performing antigen-dependent versus -independent functions  |
| pitfalls   |
| experimental outcomes are confounded by the loss of all phagocytic cells, both within and outside the kidney; as a result, DC- and Mø-dependent functions of rMoPh may not be separable, and products from rapid death of phagocytic cells may also influence immune and inflammatory responses  |

the following marker profile: CD11b<sup>+</sup> CD68<sup>+</sup>BDCA-1<sup>+</sup>CD14<sup>+</sup>DC-SIGN<sup>+</sup> CD11c<sup>+</sup>MHC II<sup>+</sup>CD207<sup>-</sup>.<sup>6,20,21</sup>

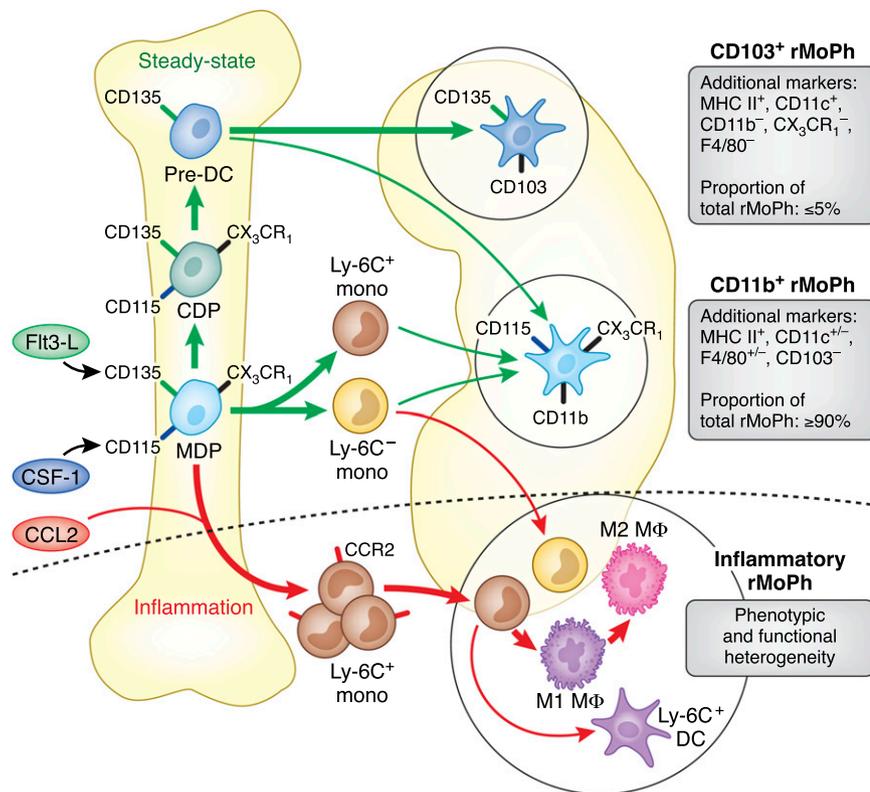
Studies of the ontogeny of resident rMoPh in mice show that both major subsets derive from a common hematopoietic monocyte/Mø/DC precursor (MDP), either through a common DC precursor, which gives rise only to pre-DCs and DCs, or through circulating monocytes (Figure 1).<sup>1,18,38</sup> Two bone marrow-derived monocyte subsets, distinguished by high or low expression of the surface protein Ly6C in mouse and expression patterns of CD14 and CD16 in humans,<sup>1</sup> may each contribute to the resident rMoPh pool at steady state (Figure 1).<sup>18,39</sup> However, circulating monocytes play a larger precursor role for the additional rMoPh populations that arise during inflammatory infiltration of the kidney (discussed below).<sup>35,40</sup> Whether

all rMoPh represent the progeny of MDP remains unclear, and recent studies of mouse and human hematopoiesis raise the possibility that some rMoPh originate from lymphoid progenitors.<sup>41</sup> The development of the renal mononuclear phagocytic system commences before nephrogenesis,<sup>42</sup> but whether vestigial, intrarenal progenitor cell niches contribute to renewal of rMoPh populations in postnatal life is unknown.<sup>1,18</sup>

The renal-derived poietins and other renal-specific factors that induce MDP lineages to rMoPh are relatively unclear. With the exception of CD103<sup>+</sup> rMoPh, activation of both the Fms-like tyrosine kinase 3 receptor (CD135) and CD115 are required for the development and maintenance of the vast majority of rMoPh (Figure 1).<sup>18,43</sup> Colony-stimulating factor 1 (CSF-1), the ligand for CD115, is expressed by the renal parenchyma<sup>44</sup> and

when injected, expands circulating monocytes.<sup>45</sup> Whether the density of rMoPh in normal kidneys also increases with CSF-1 injection is unclear, but *in vivo* blockade of CSF-1/CD115 interactions results in depletion of most resident rMoPh.<sup>43</sup> Systemic administration of Flt3L, the ligand for CD135, increases the density of rMoPh,<sup>46,47</sup> but whether Flt3L is expressed within the kidney is unknown. Nevertheless, isolated kidney stromal cells secrete other trophic factors for MDPs,<sup>48</sup> exemplifying the probable role of the renal parenchyma to differentiate the renal mononuclear phagocytic system.<sup>49</sup>

Few studies have addressed cellular turnover within the renal mononuclear phagocytic system.<sup>50</sup> Bromodeoxyuridine (BrdU) labeling and parabiosis experiments in mice show that 10% of the predominant CD11b<sup>+</sup> rMoPh in recipient



**Figure 1.** Ontogeny of the renal mononuclear phagocytic system of the mouse at steady state and during inflammation. At steady state, bone marrow–resident MDPs give rise to common dendritic cell precursors (CDPs) and pre-DCs. Pre-DCs circulate to the healthy kidney to generate CD103<sup>+</sup> rMoPh and a proportion of the resident CD11b<sup>+</sup> rMoPh. MDPs also give rise to circulating Ly-6C<sup>+</sup> monocytes and Ly-6C<sup>-</sup> monocytes, which act as additional precursors for resident CD11b<sup>+</sup> rMoPh. During renal inflammation, large numbers of Ly6C<sup>+</sup> (inflammatory) monocytes are released from the bone marrow in CCR2/CCL2-dependent fashion and enter the injured kidney along with a proportion of circulating Ly6C<sup>-</sup> monocytes. Infiltrating Ly-6C<sup>+</sup> monocytes serve as precursors for rMoPh with the characteristics of classically activated (M1) Mø and inflammatory DCs. Alternatively activated (M2) Mø arise from M1 Mø through reprogramming (plasticity). Additional work is required to determine whether M2 Mø or other inflammatory rMoPh develop directly from infiltrating Ly6C<sup>-</sup> monocytes. The growth factor axes, FIt3L/CD135 and CSF-1/CD115, important in the development of rMoPh are also shown in the figure.

mice becomes BrdU-positive within 12 hours. However, it requires 30 days for rMoPh from parabiotic donors to completely disappear after mice are separated. Of interest, turnover rates for CD103<sup>+</sup> rMoPh are approximately two times as fast.<sup>18</sup> In contrast to these experimental approaches, bone marrow transplant studies in mice suggest that repopulation of rMoPh by MDP lineages requires at least 8 weeks and possibly several months—variability that may be caused by irradiation techniques and strain of mice.<sup>19,35,51,52</sup> In any respect, these studies together suggest that

complete turnover of the renal mononuclear phagocytic system is slow at steady state.

### FUNCTIONS OF rMoPh IN SURVEILLANCE, TOLERANCE, AND TISSUE CYTOPROTECTION

Surveillance, the anatomic and functional readiness to respond to environmental cues, is well described for the renal mononuclear phagocytic system, and rMoPh are often considered sentinels of the renal immune system, responding

to diverse environmental cues that inform their subsequent functions. In the normal kidney, rMoPh are responsive to a range of stimuli associated with tissue perturbations such as pathogen-associated molecular patterns, damage-associated molecular patterns (DAMPs), other cell and matrix debris, immunoglobulin, complement components, oxygen tension, adenosine, cytokines, chemokines, and cell–cell contact.<sup>24–29</sup> Nonetheless, the specific protective roles of each surveillance mechanism and the possibilities that surveillance mechanisms differ by anatomic location or rMoPh subpopulation have not been extensively investigated to date. Additional studies are needed to increase understanding of how rMoPh respond to cues with varying characteristics and within different renal compartments.

Peripheral tolerance to self-antigens within the kidney that may escape central tolerance is also likely to be orchestrated by rMoPh. It is known that CD11c<sup>+</sup> rMoPh at steady state sample self-antigens derived from tubular filtrate, renal cells, or renal matrix.<sup>16,53,54</sup> These cells transport and present antigens to cognate T lymphocytes in renal lymph nodes, supplementing additional rMoPh-independent lymphatic transport and presentation of small filtered antigen, and promote tolerance to such antigens through mechanisms such as cross-tolerance.<sup>53,55</sup> The intrarenal sampling, transport, and presentation of antigen occur through interstitial rMoPh, and no studies to date have shown the ability of intraglomerular rMoPh to educate T lymphocytes through antigen presentation, whether to tolerance or immunity. Interestingly, rMoPh isolated from normal kidneys on the basis of CD11c expression induce the expansion of regulatory T lymphocytes in allogeneic mixed leukocyte reactions,<sup>46</sup> suggesting the possibility that rMoPh propagate regulatory T lymphocytes in the periphery at steady state *in vivo*. Aside from hypoxemia,<sup>56–58</sup> however, the cues within the kidney that may influence rMoPh to enhance or break peripheral tolerance are not well understood.<sup>54,55,59</sup>

In addition to maintaining tolerance to self-antigens, mounting evidence suggests that rMoPh at steady state also protect or lessen damage to the renal parenchyma after diverse insults through innate, anti-inflammatory responses.<sup>19,60–62</sup> This finding may reflect the innate phase response by tolerogenic rMoPh utilizing counter-regulators such as single Ig receptor-related protein,<sup>63</sup> IFN regulatory factor 4,<sup>64</sup> adenosine 2A receptor,<sup>65</sup> hemoxygenase-1,<sup>56,62</sup> and Fc  $\gamma$ -receptor.<sup>66</sup> Secretion of IL-10 by resident rMoPh is emerging as one of the key effectors of cytoprotection,<sup>61,66</sup> raising the possibility of therapeutically augmenting this secretion by rMoPh to enhance cytoprotection.<sup>30,67</sup> Additional research is needed to determine whether this function of the renal mononuclear phagocytic system represents an active response by rMoPh to silence insults that should not be perceived as injurious to the kidney, such as periods of brief ischemia or products from normal cellular turnover.<sup>68</sup>

## FROM STEADY STATE TO INFLAMMATION

Unlike rMoPh functioning at steady state, rMoPh during inflammation exhibit highly complex and dynamic responses that can determine renal outcomes after injury.<sup>30–32</sup> Studies of mouse models of acute kidney injury induced by endotoxemia, ischemia reperfusion, acute urinary obstruction, and pyelonephritis show that resident rMoPh in the interstitium increase in size, upregulate MHC and costimulatory proteins, and secrete inflammatory mediators within hours after initiating injury.<sup>15,16,69,70</sup> In some studies, an unknown fraction of resident rMoPh vacate the interstitium within 24–48 hours coincident with the accumulation of rMoPh in draining renal lymph nodes.<sup>16,71</sup> During the same interval, large numbers of Ly-6C<sup>+</sup> (inflammatory) monocytes as well as some Ly-6C<sup>-</sup> monocytes infiltrate the kidney and along with remaining resident rMoPh, undergo activation and differentiation to progeny rMoPh with

diverse functional phenotypes (Figure 1).<sup>35,40,69</sup> Bone marrow release of Ly-6C<sup>+</sup> monocytes and trafficking of these cells to the injured kidney is triggered by CCR2 ligation.<sup>40,72</sup> In glomerular inflammation, a similar influx and expansion of rMoPh, functioning primarily as M $\phi$ , is well described.<sup>73,74</sup> Whether intraglomerular rMoPh present at the initiation of injury also migrate to renal lymph nodes for antigen presentation is unknown, but glomerular infiltration by rMoPhs with the phenotype of conventional and plasmacytoid DCs has been described in human lupus nephritis.<sup>21,75</sup> In any respect, the degree to which inflammatory monocyte-derived rMoPh perform the repertoire of M $\phi$  and DC functions (Figure 1 and Table 1) within glomerular or tubulointerstitial compartments is not fully understood. In the following sections, we summarize current knowledge of the role of the renal mononuclear phagocytic system in active renal immunity and inflammation and their resolution.

## FUNCTIONS OF rMoPh IN IMMUNITY, TISSUE INJURY, AND TISSUE REPAIR

The renal mononuclear phagocytic system plays pivotal roles in proinflammatory innate and adaptive immune responses initiated within the kidney. rMoPh resident at steady state are induced to rapidly produce proinflammatory innate cytokines (TNF, IL-6, and IL-1) and chemokines (CCL2, CCL5, CXCL10, and CXCL2) depending on environmental cues.<sup>40,70,74,76</sup> As a result, Ly-6C<sup>+</sup> monocytes and other leukocytes are recruited into the kidney, providing a secondary and major source of innate mediators.<sup>35,40,74</sup> This innate phase, evident during either glomerular or tubulointerstitial inflammation, shapes subsequent adaptive immune responses by rMoPh, although this progression has been more clearly described for interstitial compared with glomerular rMoPh. For example, in models of GN, resident interstitial CD11c<sup>+</sup> rMoPh suppress T helper type 1 (Th1) lymphocytes recruited early after injury.<sup>60</sup>

With prolonged innate inflammation, likely in concert with DAMPs,<sup>77–79</sup> these CD11c<sup>+</sup> rMoPh mature and now stimulate Th1 effectors.<sup>80,81</sup> Studies in models of ureteral obstruction suggest that this pattern may also influence intrarenal Th17 responses orchestrated by resident interstitial rMoPh.<sup>69</sup> Additional research is clearly needed to define the full spectrum of immune stimulatory properties of the major rMoPh subpopulations as well as any role for intraglomerular rMoPh in adaptive immune responses.

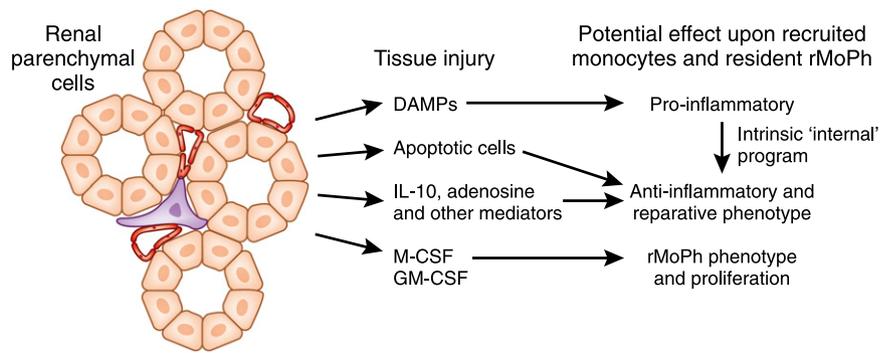
In addition to orchestrating other leukocyte populations that may induce injury, rMoPh may also directly damage the renal parenchyma. As described above, resident rMoPh elaborate damaging innate cytokines.<sup>30,40,70</sup> In addition, recruited inflammatory monocytes<sup>35,40</sup> that differentiate into inflammatory rMoPh also produce oxygen radicals, hydrogen peroxide, nitric oxide, IL-1, TNF- $\alpha$ , and other effectors of tissue injury.<sup>82–86</sup> The vast majority of reports on this acute phase of injury, whether focused on glomerular or tubulointerstitial compartments, assign responsibility for tissue damage to resident or recruited rMoPh polarized to a classically activated (M1, proinflammatory) M $\phi$  phenotype.<sup>27,30</sup> In contrast, later fibrotic phases of injury are orchestrated by resident or recruited rMoPh polarized to an alternatively activated (M2, anti-inflammatory and wound healing) M $\phi$  phenotype.<sup>29,30,87</sup>

In contrast to their role in tissue injury, rMoPh are also associated with repair of damaged renal parenchyma during resolution of renal inflammation. Seminal studies using clodronate-containing liposomes (Table 2) to ablate rMoPh show that recruited glomerular rMoPh are required for the spontaneous repair that occurs after glomerular injury in the Thy1.1 model of mesangioproliferative GN.<sup>88</sup> Ablation and adoptive transfer studies conducted later similarly showed that recruited rMoPh actively promote repair of injured renal tubules.<sup>67,87,89–91</sup> These reparative rMoPh clear DAMPs and other cell and matrix debris, stimulate proliferation of

surviving cells through elaboration of wnt ligands, and promote angiogenesis.<sup>92</sup> This biphasic response by recruited rMoPh to first injure and then repair renal parenchyma may reflect a process of reprogramming. After injury, resident and recruited rMoPh subpopulations exhibit distinct expression of proinflammatory, anti-inflammatory, profibrotic, and reparative factors<sup>35,40</sup> suggestive of the presence of heterogeneous populations of rMoPh fulfilling disparate functions. Although functional heterogeneity is undoubtedly present among rMoPh at any given time after an episode of renal injury, individual rMoPh can switch from inflammatory to reparative phenotypes within the renal interstitium,<sup>30,90</sup> a process referred to as plasticity (discussed below). Regardless of their origin, additional studies are needed to determine whether reparative rMoPh are retained after kidneys heal to comprise a long-lasting component of the renal mononuclear phagocyte system at steady state.

### PLASTICITY OF FUNCTION OF rMoPh DURING RENAL INJURY AND REPAIR

As the recent study by Lee *et al.*<sup>90</sup> illustrates, the ability of rMoPh to change functions over time may be an important general property of the renal mononuclear phagocytic system (Figure 2). Classic examples of rMoPh plasticity include the maturation of renal DCs to educate T lymphocytes and the polarization of renal Mø to M1 or M2 functional phenotypes in response to environmental cues.<sup>30,93</sup> More recent studies show that bone marrow-derived Mø or rMoPh display biphasic expression of proinflammatory factors followed by anti-inflammatory and reparative factors in response to challenge with lipopolysaccharide or ischemic injury, respectively.<sup>62,92,94,95</sup> Within the kidney, specific paracrine factors released from renal parenchymal cells, such as IL-10, DAMPs, or apoptotic bodies, initiate or augment this phenotypic reprogramming of rMoPh.<sup>90,96,97</sup>



**Figure 2.** Proposed model for plasticity of rMoPh during inflammation and repair. During inflammation, rMoPh are derived from both resident and infiltrating cells. The release of DAMPs provides a proinflammatory stimulus and activates rMoPh to produce injurious mediators such as  $\text{TNF}\alpha$ . In the absence of ongoing injury, such rMoPh subsequently undergo an intrinsic phenotypic shift with upregulation of anti-inflammatory and reparative mediators such as hemeoxygenase-1 and wnt ligands. An anti-inflammatory and reparative phenotype may also be induced by uptake of apoptotic cells or exposure to IL-10 and other mediators. rMoPh and their precursors are exposed to renal-derived poietins (e.g., CSF-1 and granulocyte macrophage colony-stimulating factor), which can influence their differentiation and functional polarization.

**Table 3.** Roadmap of key topics for future research on the renal mononuclear phagocytic system

|                                   |  |
|-----------------------------------|--|
| General                           | <ul style="list-style-type: none"> <li>identify markers that indicate specific functions of rMoPh</li> <li>delineate the functions of glomerular rMoPh from tubulointerstitial rMoPh</li> <li>correlate murine with human rMoPh subsets and functions</li> </ul> |
| Ontogeny                          | <ul style="list-style-type: none"> <li>define the precursors and factors that differentiate rMoPh subsets</li> <li>define the developmental heterogeneity of rMoPh along the nephron</li> </ul>  |
| Surveillance                      | <ul style="list-style-type: none"> <li>define the repertoire of surveillance mechanisms used by rMoPh</li> <li>define the extent of differential surveillance by rMoPh along the nephron</li> </ul>  |
| Tolerance                         | <ul style="list-style-type: none"> <li>identify the cues that enhance or break peripheral tolerance by rMoPh</li> <li>identify the subsets of rMoPh involved in peripheral tolerance</li> </ul>  |
| Tissue cytoprotection             | <ul style="list-style-type: none"> <li>identify the cues that enhance or diminish cytoprotection by rMoPh</li> <li>identify the subsets of rMoPh involved in cytoprotection</li> </ul>   |
| From steady state to inflammation | <ul style="list-style-type: none"> <li>delineate the migratory patterns and chemotactic factors for resident and recruited rMoPh</li> <li>identify the subsets of rMoPh that promote versus retard inflammation after injury</li> </ul>                          |
| Immunity                          | <ul style="list-style-type: none"> <li>define the mechanisms of antigen capture and presentation along the nephron</li> <li>define the role of resident versus recruited rMoPh in programming T lymphocytes</li> </ul>   |
| Tissue injury                     | <ul style="list-style-type: none"> <li>define the cytotoxic contribution of resident versus recruited rMoPh</li> <li>define the fibrogenic and fibrolytic contribution of resident versus recruited rMoPh</li> </ul>   |
| Tissue repair                     | <ul style="list-style-type: none"> <li>define the overlapping programs by rMoPh to support nephrogenesis and tissue repair</li> <li>define the interaction of rMoPh with tissue-resident progenitors/stem cells</li> </ul>                                       |
| Plasticity                        | <ul style="list-style-type: none"> <li>determine the differences in plasticity of resident versus recruited rMoPh</li> <li>define the molecular mechanisms of plasticity of rMoPh during injury and repair</li> </ul>  |

#### Table 4. Key conclusions

At steady state, subsets of rMoPh exist that coexpress markers previously thought to segregate M $\phi$  and DCs. These cells exhibit functional properties considered typical of both DCs and M $\phi$ .

The renal mononuclear phagocytic system performs important homeostatic and sentinel functions in the steady-state kidney and maintains immune tolerance against self- and innocuous antigens.

The renal mononuclear phagocytic system changes dramatically during injury to the kidney, with resident and recruited rMoPh exhibiting functional heterogeneity and plasticity in defense against microbes, mediation of parenchymal injury, and promotion of tissue repair.

The plasticity of rMoPh may also represent inducible reactivation of developmental programs normally active in differentiating precursors. For example, pre-DCs are the immediate precursors for CD103<sup>+</sup> rMoPh; however, pre-DCs can also be induced to repopulate CD11b<sup>+</sup> rMoPh.<sup>18</sup> The former progeny functions solely as DCs, although this finding has not been formally shown within the kidney, whereas the latter progeny clearly harbors subsets performing functions as M $\phi$ .<sup>18</sup> The balance of poietins produced within the kidney for rMoPhs, particularly during inflammation or its resolution, may be a key driving force for this altered lineage commitment.<sup>44</sup> Intriguingly, although no studies have been done on rMoPh *per se*, emerging evidence suggests that intrinsic molecular programs of plasticity governed by microRNA (miRNA)<sup>98</sup> determine the commitment and transition of rMoPh to function as DCs or M $\phi$ . In addition, studies of bone marrow-derived M $\phi$  suggest that epigenetic chromatin modification by histone-modifying enzymes,<sup>99,100</sup> and gene-silencing polycomb group proteins<sup>101</sup> may be key regulators of M $\phi$  activation status. Future research on plasticity within the renal mononuclear phagocyte system may help to develop a unifying nomenclature that represents the function of rMoPh.

#### A ROADMAP FOR FUTURE PROGRESS

Significant progress in understanding the renal mononuclear phagocytic system has been achieved over the past three decades. Many typical DC and M $\phi$ -associated functions of the major rMoPh subsets have been described,

especially in the last 5 years. As this brief review highlights, however, rMoPh may fulfill definitions and functions both of DCs and M $\phi$ , hampering definitive classification. Indeed, parallel streams of literature have been created that do not provide a fully integrated body of knowledge to this point. As a roadmap for future research, we highlight in Table 3 some of the specific areas of investigation that may yield valuable new insights. Engaging in this roadmap will require acknowledging that the complexity of the renal mononuclear phagocytic system, as with the mononuclear phagocytic system in general,<sup>5</sup> does not fit well with simple, binary naming conventions. Specifically, historic divisions that have separated renal investigators into M $\phi$  and DC camps are falling, allowing for some key unifying conclusions to be made (Table 4) and paving the way for novel, joint approaches to better understand the role of the renal mononuclear phagocytic system in health and disease of the kidney.

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#### DISCLOSURES

None.

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