Monocytes and Macrophages in Kidney Transplantation and Insights from Single Cell RNA-Seq Studies

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Abstract
Single-cell RNA sequencing (scRNA-seq) is a powerful technology that allows for the identification of minority cell types in complex tissues, such as immune cells in the kidney. Previously, gene expression from infrequent cell types was missed using bulk RNA-sequencing methods due to an averaging effect. Additionally, scRNA-seq facilitates assignment of cell origin in a sample, a shortcoming of previous bulk sequencing technologies. Thus, scRNA-seq is ideal to study the immune cell landscape and the alloimmune response in the human kidney transplant. However, there are few studies published to date. Macrophages are known to play an important role in health and disease in the kidney. Furthermore, it is known that macrophages play key roles in rejection of the kidney transplant. The definition, ontogeny, and function of these cells is complex and nomenclature has evolved as new technologies have become available. In this review, an overview is provided of monocyte and macrophage nomenclature, ontogeny, and function, with a specific focus on kidney transplantation, and including novel scRNA-seq findings. scRNA-seq offers an unbiased transcriptional approach to defining macrophages and provides insights into macrophage ontogeny and function not possible with contemporary methods.

Introduction
Monocytes and macrophages are categorized as mononuclear phagocytes (1). This group of cells can be defined on the basis of functional and phenotypic characteristics (2). Macrophages are larger cells with vacuoles that specialize in phagocytosis and clearing of apoptotic cells, debris, and pathogens. Monocytes make up about 10% of nucleated blood cells and play a role in responses to injury and infection by migrating into tissues. It was thought that monocytes from the blood compartment were the sole source of tissue-resident macrophages. However, this is not the case, as will be discussed later. Our understanding of the macrophage continues to evolve and has revealed more complexity with the application of modern experimental methods. For example, the introduction of polychromatic flow cytometry enabled detailed phenotyping of mononuclear phagocytes that can now be characterized by expression of discrete surface proteins. This ultimately led to the identification of multiple subsets of monocytes, and macrophages (3,4). These populations are heterogeneous and will be discussed below. This review will focus on renewed perspectives on these cells and the associated single-cell RNA-sequencing (scRNA-seq) data from native and transplanted kidneys.

Monocytes
Monocytes are innate immune cells that play a central role in antimicrobial defense by direct phagocytosis of pathogens, cytokine release, and communication with other immune cells. On the basis of flow cytometry, human monocytes can be defined by their relative expression of CD14 and CD16. Classic monocytes express CD14 and no CD16, whereas nonclassic monocytes predominately express CD16. These human markers of classic and nonclassic monocytes are equivalent to Ly6ChiCD43lo monocytes and Ly6CloCD43hi monocytes in mice, respectively (5). These two monocyte populations are not discrete, and an intermediate monocyte has been described that expresses both CD14 and CD16 at lower levels than classic and nonclassic monocytes. Some have suggested that these intermediate monocytes can be defined by degree of HLA-DR expression (6). However, in terms of monocyte function, most conclusions are made on the basis of data from mouse studies using Ly6C±CD43hi monocytes and Ly6C±CD43hi monocytes in mice, respectively (5). These two monocyte populations are not discrete, and an intermediate monocyte has been described that expresses both CD14 and CD16 at lower levels than classic and nonclassic monocytes. Some have suggested that these intermediate monocytes can be defined by degree of HLA-DR expression (6). However, in terms of monocyte function, most conclusions are made on the basis of data from mouse studies using Ly6C±CD43hi equivalent and Ly6C±CD43hi equivalent. The primary function of Ly6C± cells, which may be terminally differentiated blood-resident macrophages, is to survey endothelial integrity. In contrast, the function of Ly6C± monocytes is poorly understood and likely related to their high phagocytic capacity and ability to migrate into sites of tissue inflammation (7,8). In steady state conditions,
monocytes do not maintain resident macrophage populations (except in specific conditions). During an inflammatory response to a pathogen or toxin, Ly6Chi cells enter the interstitium and give rise to resident macrophages. These monocyte-derived macrophages respond to tissue microenvironmental cues and differentiate into macrophage subphenotypes to drive, or resolve, inflammation and repair tissue.

**Macrophages**

Macrophages populate all mammalian organs and can self-maintain for long periods of time. They are best known as immune sentinels, but also preserve tissue homeostasis by performing tissue-specific functions and adapting to phenotypic changes (9–11). Similar to monocytes, macrophages are not a homogenous population of cells and, upon activation, they polarize into various phenotypes. Studies in mice have defined both an M1 and M2 phenotype in Balb/c and C57BL/6J mice. Macrophages activated by IFN-γ were defined as classic macrophages, and those activated by IL-4 as alternative macrophages (12–14). The M1 macrophages have been described as proinflammatory and M2 macrophages as promoters of tissue repair (15). It must be noted that terms used to describe macrophage subtypes are inconsistent and not comparable. For example, M1 is not synonymous with "classic" when referring to macrophages. In an effort to move away from confusing terminology and create a reproducible in vitro experimental standard, Murray et al. (16) proposed macrophages be defined by the activator, i.e., M(IL-4), M(Ig), M(IL-10), M(GC), M(IFN-γ), and M(LPS). Most classification work was performed in vitro on murine cells, leading to further confusion because in vitro-stimulated surface markers do not translate to in vivo models. There was little overlap in gene expression from LPS-treated peritoneal macrophages with in vitro LPS/IFN-γ–stimulated macrophages (17–19). Xue et al. (20) examined the transcriptional responses of human macrophages stimulated by diverse signals and found a spectrum of macrophage activation states based on gene expression response. Using their human gene expression data, the authors of this study sought to define a core set of human macrophage markers that are independent of activation state. This approach identified cell surface markers (CD14, FCGR2A, CD163, CD206, CD209, FcεR, Dectin1) that discriminated human macrophages from dendritic cells and CD14+ monocytes by flow cytometry.

**Macrophages in the Kidney**

Macrophages are tissue-resident cells and do not recirculate. Fate-mapping studies in mice have established that tissue-resident macrophages are seeded prenatally from yolk sac–derived progenitor cells (2). Circulating monocytes can take residence on entry into tissues. They then acquire the self-maintenance capacity, tissue-specific transcriptomic identity, and functional specialization of their resident embryonic counterparts (21). Thus, tissue-resident macrophages are composed of a mixed source of cells,
those that are yolk sac derived and monocyte derived (Figure 1). In adults, bone marrow–derived monocytes rarely invade healthy kidney and are found at low levels (22). However, when the kidney becomes injured or inflamed, monocyte infiltration increases and bone marrow–derived cell engraftment occurs (23,24). In this setting, infiltrating monocyte-derived macrophages drive a proinflammatory response. In kidney, tissue-resident macrophages have been shown to be involved in the resolution of infection, and progression to fibrosis (25).

Due to the diverse roles that macrophages of different origins play, it would be important to identify macrophage subtype and origin in the kidney. There are well-defined markers in mice, but this is not the case for humans. For example, one of the markers used to define tissue-resident macrophages in the murine kidney, Adgre1, is not expressed in human tissue macrophages (26,27). This major barrier in translating findings from mouse studies to humans was addressed by Zimmerman et al. (28) in recent work that used scRNA-seq to identify common tissue-resident kidney macrophage markers in multiple species, including humans. They performed scRNA-seq on kidney tissue from 8-week-old C57BL/6 male mice, a 3-month-old male Sprague–Dawley rat, a 6-month-old male pig, and normal human kidney. The authors enriched for innate immune cells (CD45+, B cell−, T cell−) from the single-cell digestion preparations. They used canonical markers for innate cells from the literature to define cell types. In mouse kidney, infiltrating macrophages were identified by Ccr2 and Il17a expression. Resident macrophages were identified by Adgre1 and Fcgr1 expression. Infiltrating macrophages were further subdivided into Ly6chi (Ly6c1, Ly6c2) and Ly6clo (Cebp, Nr4a1) subpopulations. The authors looked for genes differentially expressed between cell types/clusters and identified the uniquely expressed markers Chil3 and Plac8 in Ly6c1, Fdnp4 and Ear2 in Ly6clo infiltrating macrophages, and C1qc and Cd81 in embryonic-derived resident macrophages. Intriguingly, authors examined scRNA-seq data from their rat, pig, and human samples and also found a unique cluster of C1q enriched cells in each species. Cd81, C4d74, and Apoe genes were also exclusively enriched in these clusters. Therefore, the authors defined a set of discriminatory gene markers, C1qc and Cd81, for resident kidney macrophages conserved across species. A notable finding from their studies was that canonical markers used to identify macrophages in human samples (CD68, CD163, CD14, FCGR3A) were not specific to human renal macrophage populations and could not discriminate human infiltrating or resident macrophages.

scRNA-seq analysis was applied to investigate the spatial and temporal zonation of macrophages in the human kidney (29). Stewart et al. (29) studied 14 adult human kidneys and six human fetal kidneys (gestational age 7 through 16 weeks). Their analysis created a tool to predict the depth of each sample, defined as either cortex, corticomedullary, or medullary. They found that macrophages were enriched in the medulla and present from the earliest time point studied. The authors hypothesize that this distribution of macrophages is related to bacterial infection prevention in the postnatal kidney. Using a subclustering approach, they described four mononuclear phagocyte subtypes (MNP-a/b/c/d), all of which expressed ITGAX (CD11c) and HLA-DRA. These four clusters were vaguely defined by the authors but CD14 and FCGR3A (CD16) expression was predominant in MNP-a and MNP-b, respectively. The authors defined the MNP-d cluster as tissue resident on the basis of RUNX1 expression. Interestingly, C1QC and MRC1 were also predominantly expressed in MNP-d cells, consistent with the findings of Zimmerman et al. (28). Furthermore, MNP-d was the only adult macrophage cluster with transcriptional similarity to a fetal kidney macrophages, both expressing C1QC and MRC1, consistent with tissue-resident status in the adult kidney.

Arazi et al. (30) studied the immune cell landscape in patients with lupus nephritis. This study included a large number of samples (34) but used older technology, which yielded fewer cells (31). They subclustered 466 myeloid cells into five clusters (CM0–4) and concluded three of these clusters were infiltrating macrophages. The authors describe C1Q expression in two of these three clusters, which is now known to be a marker of tissue-resident macrophages, as described above. Thus, the conclusions drawn from this study are not consistent with other scRNA-seq studies.

Macrophage Ontogeny in Kidney Transplantation

The first report of scRNA-seq analysis of cells from a rejecting human kidney biopsy specimen revealed two clusters labeled monocyte 1 and monocyte 2 (32). With hindsight, these clusters would be more appropriately labeled macrophages. These two clusters were defined by FCGR3A and FCN1 expression, respectively, which was validated by immunohistochemistry and immunofluorescence of independent rejection samples. Monocyte 1 cells are tissue-resident macrophages because they uniquely expressed C1Q genes, and monocyte 2 cells are infiltrating macrophages because they expressed PLAUR, as defined subsequently by Zimmerman et al. (28). Interestingly, our analysis suggested that resident macrophages (monocyte 1) were developing a dendritic cell–like phenotype because they differentially expressed SDC3, ABCA1, APOE, PDE3A, IGKC, LGMN, and CD83 (33–37). Thus, tissue-resident macrophages may play a role in (allo)antigen presentation in the setting of kidney transplantation.

Determining cell origin in human tissues has been limited to the study of sex-mismatched transplant patients and relied on sex-chromosome analysis using fluorescence in situ hybridization or expression of sex-specific genes (38–40). These studies were not able to discriminate between individual cell types (unless purified from a secreted source, such as BAL). Recently, our group performed scRNA-seq on kidney transplant biopsy specimens and harnessed expressed single nucleotide variants (SNVs) to determine the origin of each cell (41). We performed whole-exome sequencing of donor and recipient germline DNA to use as reference sets of coding SNVs. We focused on immune cells from our samples and found the median number of SNVs overlapping at least one read per cell ranged between 78 and 233. Using this approach, we found approximately 50% of kidney macrophages were of donor origin in the nonrejecting kidney transplant. These
donor-derived macrophages differentially expressed CIQC and CD81, confirming they were tissue resident. In the setting of rejection, the proportion of donor macrophages dropped to <2%. Thus, infiltrating monocyte-derived cells filled the macrophage niche during rejection. Biopsy specimens taken before and after rejection from one patient in our study suggested tissue-resident donor macrophages can repopulate the kidney allograft once the rejection has resolved. It is important to note this study included only five biopsy samples taken at various times post-transplant. Thus, whether the donor macrophage population varies independently of time post-transplant or can repopulate postrejection needs to be verified independently. To better understand tissue-specific gene expression patterns of resident donor macrophages in kidney allografts, we performed a pathway analysis of genes differentially expressed in donor macrophages and found MHC class II antigen presentation and processing pathways were significant. However, donor macrophages also differentially expressed genes previously described in wound-healing macrophages or M2 macrophages, such as MRCI (CD206), STAB1, CLEC4A, and IGF1. It seems that the tissue-resident macrophage population in the kidney transplant setting is heterogeneous, which could be driven by differences in the microenvironment present during rejection.

**Macrophage Function in the Transplanted Kidney**

It has been known for a long time that macrophages play a role in kidney allograft rejection (42). Macrophages can account for up to 60% of immune cells in severe kidney transplant rejection (43). In fact, macrophages are found in both acute cell-mediated rejection and antibody-mediated rejection (44,45). Additionally, macrophages have been implicated in both human and mouse models of chronic allograft injury, which are characterized by progressive tubular atrophy, and interstitial fibrosis. Detection of fibrosis across kidney allograft biopsy specimens is the result of ongoing alloimmune injury, and other nonimmune insults (46). Toki et al. (47) investigated the role of CD68⁺ CD206⁺ macrophages in kidney transplant rejection and found increased macrophage numbers correlated with increased whole-tissue inflammatory gene expression and worse allograft outcome. The authors described these macrophages as infiltrating, however, insufficient data was provided to determine origin.

Previously, studies of innate immunity in transplantation relied on specific cellular markers and genetic tools to test a priori hypotheses. Dangi et al. (48) demonstrated the power of scRNA-seq to interrogate macrophage function in an unbiased fashion using a murine model of kidney transplantation. In their combined dataset from six kidneys, they identified four macrophage and monocyte clusters. Macrophages were defined by Ifi1, Apace, Axl, and Clqhc expression and monocytes by Lyc2 and Cybb expression. The highlight of this work was the use of RNA velocity and pseudotime on monocytes and macrophages. This bioinformatics tool assumes each cell in a cluster represents a random point along an activation spectrum specific for that cell type. Thus, cells can be placed along a trajectory or pseudotime. These analyses showed Axl promotes intragraft differentiation of inflammatory macrophages and drives rejection in kidney allografts. This finding was validated at the protein level using FACS and by using Axl knockout kidney allografts. The total number of Axl⁺ macrophages, and their level of Axl expression, were substantially higher in rejecting kidneys compared with tolerantized kidneys.

Whether myeloid cells can develop memory to alloantigens independently of the adaptive immune system was explored by Dai et al. (49). They showed that murine monocytes (F4/80⁺) and macrophages (F4/80⁺) can retain memory to allogenic MHC-I via PIR-A receptors. Blocking PIR-A in transplant recipients blocked this memory response and attenuated kidney rejection. These data adds to our understanding of macrophage function in the setting of kidney transplantation. However, whether this memory response and subsequent rejection is specific to tissue-resident macrophages is not clear from this study.

**Applications, Limitations, and Future Directions of scRNA-Seq in Kidney Transplantation Research**

A major advantage of scRNA-seq over previous gene analysis methods is the ability to identify rare cell types and examine their gene expression. Previously, genes expressed from rare cell types would be lost due to averaging effects, as seen with microarray data. Another major advantage is the ability to identify T cell or B cell clones, quantify their abundance, and examine the associated gene expression. The ability to determine the degree of chimerism in a kidney transplant sample allows for the accurate analysis of immune cell origin, something difficult to do with older methods.

There are many pitfalls and limitations with scRNA-seq. Currently, most scRNA-seq studies are limited by small sample number. This is primarily due to the high cost of this technology. Interpretation of data generated from a scRNA-seq experiment also presents a huge challenge. With current technologies, <30% of transcripts per cell are captured. Many of these transcripts are highly expressed housekeeping genes or stress-related genes. Therefore, genes encoding traditional cell type “markers” are frequently not captured, making it difficult to define cell types a priori. This is particular challenging when studying immune cells in transplantation. Another issue is the temptation to define “new” cell types in a single-cell experiment. By varying function parameters and other variables used during the bioinformatic processing of data, one can potentially find as many cell clusters as desired. Therefore, careful attention to biologic plausibility is required when making conclusions from scRNA-seq data. Optimal scRNA-seq workflow requires immediate preparation of samples. However, diagnoses made from kidney transplant biopsy specimens are usually not available immediately. Therefore, samples must be frozen for later use to study a biopsy sample with a known diagnosis. This approach is only compatible with single-nucleus RNA-seq. Studies have demonstrated lower yield of immune cells (affecting lymphocyte yield more so than macrophage yield) from kidneys studied using a single-nucleus RNA-seq approach (50,51). This issue of lower immune cell yield has not been
confirmed for biopsy cores or kidney transplant samples. The field of single-cell analysis continues to move quickly, and other single-cell methods are available. For example, spatial analysis of tissues at single-cell resolution is now possible and is a powerful complement to scRNA-seq. This can be performed at the protein level (e.g., CODEX) or at the transcript level (e.g., 10X Visium or MERFISH).

Conclusions

Macrophages and monocytes have a complex ontogeny and varied functional roles. These cells display a high degree of plasticity, with phenotypes and functions likely driven by the local environment. Resident macrophages of the kidney can be identified by the common markers CD81 and CD163. In the kidney transplant setting, donor-derived tissue-resident macrophages vary in number and role. As scRNA-seq becomes more widely available, a better understanding of macrophages in their local environment will be realized and leveraged for description of physiologically relevant immune mechanisms.

Disclosures

A.F. Malone reports having ownership interest in AstraZeneca, and serving as a scientific advisor for, or member of, CareDx.

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Author Contributions

A.F. Malone conceptualized the study, wrote the original draft, and reviewed and edited the manuscript.

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