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Origin and Heterogeneity of Tissue Myeloid Cells: A Focus on GMP-Derived Monocytes and Neutrophils

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Abstract

Myeloid cells are a significant proportion of leukocytes within tissues, comprising granulocytes, monocytes, dendritic cells, and macrophages. With the identification of various myeloid cells that perform separate but complementary functions during homeostasis and disease, our understanding of tissue myeloid cells has evolved significantly. Exciting findings from transcriptomics profiling and fate-mapping mouse models have facilitated the identification of their developmental origins, maturation, and tissue-specific specializations. This review highlights the current understanding of tissue myeloid cells and the contributing factors of functional heterogeneity to better comprehend the complex and dynamic immune interactions within the healthy or inflamed tissue. Specifically, we discuss the new understanding of

the contributions of granulocyte-monocyte progenitor–derived phagocytes to tissue myeloid cell heterogeneity as well as the impact of niche-specific factors on monocyte and neutrophil phenotype and function. Lastly, we explore the developing paradigm of myeloid cell heterogeneity during inflammation and disease.

INTRODUCTION

Our immune system relies heavily on innate cells that exist in the circulation and tissues, where they constantly survey their surroundings for foreign microbial threats, tissue perturbations, and injuries. Due to their anatomical location, innate cells are the first cells that sense and encounter the anomaly to react quickly for containment, elimination, and repair. Neutrophils, monocytes, and macrophages are key players, performing both similar and unique complementary effector functions throughout homeostasis and inflammation. Neutrophils are early responders of inflammation, and they function in large swarms while secreting copious amounts of antimicrobial products and generating powerful neutrophil extracellular traps (NETs) against bacterial, fungal, and even viral pathogens (1–4). On the other hand, monocytes perform dual roles by not only participating in antimicrobial activities but also performing additional roles in tissue repair and resolution when they differentiate into monocyte-derived macrophages. As key tissue sentinel cells, macrophages are present across various organs throughout the body and are involved in complex processes, including neurogenesis, angiogenesis, osteogenesis, and erythropoiesis, indicative of their unique ability to adapt and contribute to their place of residence.

Unlike lymphoid lineage–derived cells, most myeloid cells generally have a high turnover rate and are promptly mobilized upon pathogen detection. Tissue-resident myeloid cells, such as macrophages and mast cells, are exceptions, as they have long life spans while performing their homeostatic functions (5). With the emergence of single-cell technologies and new fate-mapping models, the field of monocyte-macrophage ontogeny, heterogeneity, and function has been extensively refined and revised (6, 7). These findings illuminate the embryonic origin of most resident tissue macrophages (RTMs) and the crucial role their niche of residence plays in their programming, which has also led to a better understanding of the differentiation of monocyte-derived macrophages recruited in tissues at steady state and monocyte-derived phagocytes during inflammation. Specifically, the ontogenic and niche framework of RTMs has underscored the contribution of functional heterogeneity through developmental origins and maturational stages. These studies have demonstrated that most RTMs are of embryonic origin, with notable exceptions in some barrier tissues such as the gut and dermis (8–13). Similarly, numerous overlapping studies have illuminated the understanding of neutrophil ontogeny by identifying distinct developmental states and committed neutrophil progenitors (14–21). Recent studies further indicate that neutrophil developmental stage and altered mobilization of bone marrow neutrophil populations may contribute to neutrophil functional heterogeneity, despite the mechanism underlying such heterogeneity being less well-defined than its mononuclear phagocyte counterparts (3, 22, 23). Emerging evidence also suggests that, like RTMs, neutrophils can acquire specialized roles imprinted by the tissue microenvironment, revealing a previously underappreciated complexity related to neutrophil heterogeneity, as these cells were traditionally believed to be short-lived and devoid of diversity (24–28).

Therefore, this article presents an overview of how differences in origin and tissue/niche imprinting can add to the complexities in the phenotypical and functional heterogeneity of myeloid cells during health and disease by reviewing and discussing these recent important discoveries (**Figure 1**). Notably, we outline the current concepts and competing views derived from mouse

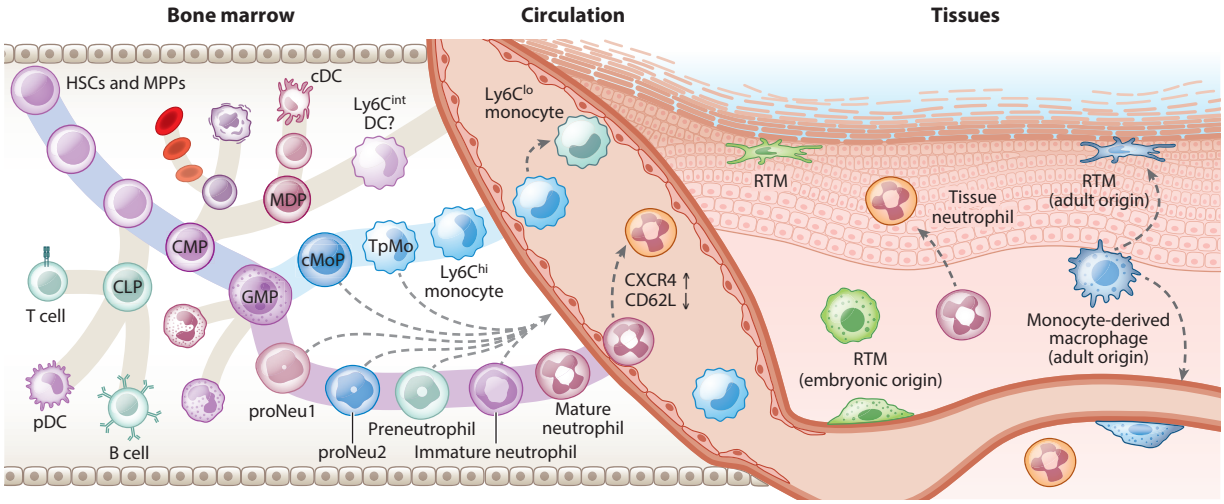

Figure 1

The landscape of myeloid cell heterogeneity. Myeloid cells develop in the bone marrow and spleen through a series of developmental intermediates stemming from hematopoietic stem cells and multipotent progenitor cells. Myeloid cells are first derived from the common myeloid progenitor, bifurcating from the lymphoid lineage, which is reliant on the common lymphoid progenitor, although single-cell transplantation and colony assays challenge this simple dichotomy. The major myeloid cells, neutrophils, and monocytes, branch off from a common granulocyte-monocyte progenitor, dictated by key transcription factors leading to the development and maturation of each myeloid cell type. Multiple studies from several groups have recently delineated the neutrophil developmental trajectory from the granulocyte-monocyte progenitor (15–21). Proneutrophils (proNeu1s and proNeu2s) are the first committed progenitors, having enhanced colony-forming properties and high proliferative abilities. They give rise to late committed and proliferating precursors called preneutrophils before maturing into immature and mature subsets. The common monocyte progenitor similarly develops into a late proliferative transitional premonocyte precursor before maturing into Ly6C^{hi} monocytes. Each developmental intermediate has the potential to be released into the circulation during inflammation (*gray arrows*, *left*), which increases the diversity of myeloid cell phenotypes and functions observed in the circulation and peripheral tissues. Once in the blood, neutrophils age, increasing CXCR4 expression, which is used to home to tissues for their clearance. Monocytes further mature in the blood, becoming Ly6C^{lo} monocytes, or differentiate into resident tissue macrophages after their recruitment to certain tissues only (small intestine lamina propria and dermis are examples of the most-studied niches) in steady state, adopting tissue-specific phenotypes according to their local niche signals. In contrast, upon an inflammatory challenge, Ly6C^{hi} monocytes recruited at the site of inflammation differentiate into monocyte-derived phagocytes that are distinct from the resident tissue macrophages that inhabit the tissues before the inflammatory challenge. Thus, heterogeneity exists at various stages of the myeloid cell life cycle and should be carefully considered. Abbreviations: cDC, conventional DC; CLP, common lymphoid progenitor; cMoP, common monocyte progenitor; CMP, common myeloid progenitor; DC, dendritic cell; GMP, granulocyte-monocyte progenitor; HSC, hematopoietic stem cell; MDP, monocyte and DC progenitor; MPP, multipotent progenitor; pDC, plasmacytoid DC; proNeu, proneutrophil; RTM, resident tissue macrophage; TpMo, transitional premonocyte. Figure adapted from images created with BioRender.com.

studies about the development of monocytes and neutrophils. We also discuss the homeostatic and disease-promoting effects of myeloid cells in tissue and peripheral sites, as well as their expansion in medullary or extramedullary sites. In addition, we provide an overview of how differences in origin and tissue/niche imprinting can add to the complexities in the functional heterogeneity of myeloid cells during health and disease. We end by exploring how the reprogramming of myeloid cells by local and systemic stimuli may lead to various inflammatory conditions.

ONTOGENY OF MYELOID CELLS: THE GRANULOCYTE-MONOCYTE PROGENITOR

It is well established that, during embryo development, the first hematopoietic progenitors emerge from the yolk sac hemogenic endothelium. Specifically, studies have shown that erythro-myeloid

progenitors develop in the yolk sac and differentiate locally into yolk sac macrophages. They can also colonize the fetal liver, where they can differentiate and give rise to myeloid cells, including fetal erythrocytes, monocytes, macrophages, and granulocytes (29–32). In fetal liver hematopoiesis, the appearance of cells phenotypically and morphologically resembling bone marrow–derived monocytes can be observed in two distinct sources (33). A "late" population of erythro-myeloid progenitors is the main source for fetal monocytopoiesis, giving rise to macrophages that populate most tissues (29, 30). Another source stems from hematopoietic stem cells (HSCs) developed in the aorta-gonad-mesonephros. These HSCs colonize the fetal liver at embryonic day 10.5 (E10.5) and similarly give rise to monocytes and granulocytes for tissue homeostasis and development (34–36), although the contribution from this source appears minor.

The current paradigm suggests that, in adult hematopoiesis, all leukocytes are derived from HSCs. These HSCs divide and differentiate into multipotent and lineage-restricted progenitors that undergo commitment and proliferation to generate a large number of progeny (37, 38). Moreover, steady-state myelopoiesis is believed to be primarily contributed by a combination of multipotent and lineage-restricted progenitors, with a minimal contribution from long-term HSCs (39, 40). Pietras et al. (41) demonstrated that discrete subsets of multipotent progenitors have distinct differences in lineage and repopulation potential. Myeloid-biased MPP3 progenitors then further develop into common myeloid progenitors (CMPs) and granulocyte-monocyte progenitors (GMPs).

GMPs were first described by the Weissman group who reported a CD16/32^{hi} population of myeloid progenitors devoid of erythrocyte and megakaryocyte differentiation potential by in vitro colony assays (42). This progenitor subset, giving rise to both granulocytes and monocytes, was later shown to require the transcription factor *Cebpa* for its development from CMPs (43, 44). A specific restricted monocyte and dendritic cell (DC) progenitor (MDP) was further isolated from GMPs and proved to be critical for monocyte production. Phenotypically different from GMPs (CD34$^+$CD16/32$^+$FLT3$^+$CX3CR1$^+$ in MDPs versus CD34$^+$CD16/32^{hi}CX3CR1$^-$CD135$^-$ in GMPs), the differentiation potential of MDPs was shown to be restricted to monocytes, macrophages, and DCs (45). Using a CX3CR1 reporter model, Auffray et al. further refined MDPs to be CX3CR1$^+$CD115$^+$CD135$^+$ (45, 46). Since MDPs did not possess neutrophil differentiation potential, they were believed to be derived from GMPs losing neutrophil potential (47, 48). However, through adoptive transfer experiments and in colony cultures, a study showed that MDPs exhibited significant granulocyte potential (49). Such discrepancy may be due to the time points chosen for analysis being too late to observe the granulocyte formation or to the isolation method leading to loss of granulocytes. Nevertheless, from MDPs, the committed monocyte progenitor (cMoP) was discovered to solely give rise to monocytes (47). By then, the CMP-GMP-MDP-cMoP-monocyte hierarchal model of monopoiesis had been established (50, 51). These monocyte-lineage progenitors were defined by multi-parametric surface markers, key transcription factors that govern their cell fate, and clonal assays that support this model (47, 48, 52).

However, recent studies have challenged this hierarchal model suggesting that cell fate decisions might occur earlier than expected. The advent of single-cell RNA profiling enabled the field to understand cell fate and commitment in the multipotent myeloid progenitors with an unprecedented level of precision and resolution (53–55). In a seminal study, data from Amit's group revealed the high level of heterogeneity within the myeloid progenitors, showing evidence of lineage priming in CMPs and GMPs through the detection of key lineage-restricted transcription factors such as *Mcpt8* (basophils), *Irf8* (monocytes), and *Gfi1* (neutrophils) (55). This evidence suggested that monocyte development can arise from the CMP stage. Of note, Yáñez et al. (56) noticed that CMPs and MDPs are Flt3$^+$ (FMS-like tyrosine kinase 3 positive) while

GMPs are Flt3$^-$, suggesting that if the existing model is correct, the progenitors first downregulate the expression of Flt3 (from CMPs to GMPs) and rapidly upregulate it (from GMPs to MDPs) again in a relatively short time. This raised the question whether MDPs were truly derived from GMPs. Using in vivo spleen transfer experiments, the group showed that MDPs are not progenies of GMPs but were directly derived from CMPs (56). We confirmed this finding by utilizing the *Ms4a3^{Cre}Rosa^{TdT}* GMP fate-mapping model, which marks GMP-derived cells (57). In particular, we identified *Ms4a3* as a specific gene expressed by GMPs (marks ~69% of GMPs) and subsequently generated *Ms4a3^{TdT}* reporter, *Ms4a3^{Cre}*, and *Ms4a3^{CreERT2}* fate-mapping models that efficiently traced monocytes and granulocytes, but not lymphocytes or tissue DCs (57). Through this model, we uncovered that MDPs were not labeled, and adoptive transfer of unlabeled GMPs (~31%) fully gave rise to *Ms4a3*$^+$-labeled progenies. Thus, together with Yáñez et al. (56), we conclusively demonstrated that MDPs are not derived from GMPs.

The divergence of CMPs into MDPs and GMPs in the recently revised model of monocyte development raises the question of the hierarchical order of cMoPs with respect to the monocyte development pathway, as cMoPs were initially described to derive from MDPs (47). Using our *Ms4a3^{Cre}Rosa^{TdT}* GMP fate-mapping mouse model, it is evident that cMoPs are the progeny of GMPs and that the cMoP is the primary progenitor contributing to the generation of monocytes in adult hematopoiesis (57). Thus, this finding suggests that the cell population discovered by Hettinger et al. (47), demarcated as CD117$^+$CD115$^+$CD135$^-$Ly6C$^+$CD11b$^-$ cells, likely contained contaminated CD115$^+$ CMPs producing cMoPs. Notably, MDPs are capable of generating cells with a monocyte phenotype without a cMoP intermediate (57). Such cells originating from this pathway may comprise the GM-CSF (granulocyte-macrophage colony-stimulating factor)-expanded R2 monocytes retaining Flt3 expression akin to MDPs (58) or blood monocytes expressing Flt3 (59) that are rather phenotypically reminiscent of CD11c$^-$ DC progenitors compared to monocytes. In line with this, Sathe et al. (49) previously reported that the cell type derived from MDPs in the presence of GM-CSF closely resembles a monocyte-derived DC (**Figure 2**).

In contrast, comparing unmethylated CpG DNA with lipopolysaccharide (LPS) stimulation, Yáñez et al. (56) observed that monocytes can be differentially derived from two distinct committed monocyte progenitors. Adoptive transfer experiments of GMPs or MDPs, along with CpG and LPS stimulation, showed the specific expansion of MDPs into Ly6C^{hi} monocytes and CD11b$^+$ conventional DCs (cDCs) through CpG. LPS instead showed the expansion of GMPs, giving rise to both Ly6C^{hi} monocytes and neutrophils without the appearance of cDCs. They thus proposed that monocytes arise from GMPs via an alternative monocyte progenitor and have a neutrophil-like phenotype with increased granule genes, including *Elane*, *Prtn3*, and *Ctsg*, closely resembling the Ym1$^+$Ly6C^{hi} monocyte subset expanded during LPS stimulation with neutrophilic genes such as *Ltf* and *Mmp9* (60, 61). From their proposed working model, cMoPs produce monocytes with the capacity to differentiate into monocyte-derived DCs (56) (**Figure 2**). Notably, their model is not fully supported by the results of single-cell analyses of bone marrow reported by other groups, as these analyses similarly failed to identify two separate monocyte progenitors (53, 56, 62, 63). However, it is noted that such approaches might not have the required resolution and sequencing depth to discern this conclusively. Rather, Yáñez and coworkers may have observed a phenomenon unique to CpG stimulation, which could explain these discrepancies with previous investigations. While Yáñez's study presented a different model, their investigations still demonstrated that GMP-derived monocyte progenitors constitute the primary source of Ly6C^{hi} monocytes (56). Furthermore, almost complete tagging of *Ms4a3^{TdT}* on Ly6C^{hi} and Ly6C^{lo} monocyte subsets in the bone marrow and blood of the GMP fate-mapping model provides the most substantial evidence to show that monocytes are mainly derived from cMoPs, reinforcing the notion that cMoPs

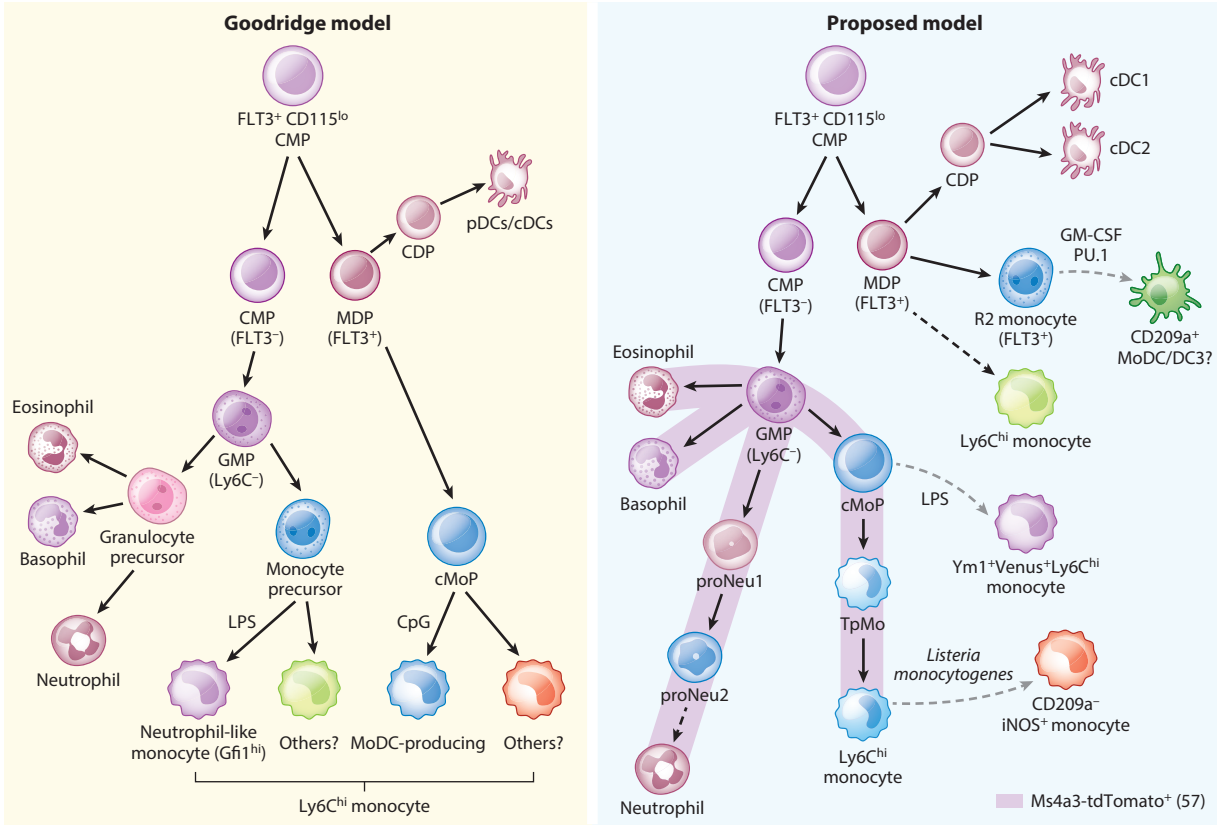

Figure 2

A consensus of myeloid cell ontogeny. Two models of myeloid cell ontogeny have been proposed. In the model presented by the Goodridge group (56) (*left*), monocytes are proposed to be derived from two distinct progenitors, GMPs and MDPs, with GMPs giving rise to a monocyte progenitor, distinct from cMoPs, which give rise to neutrophil-like monocytes. Alternatively, cMoPs give rise to monocytes capable of differentiating into MoDCs under certain stimulation. With a recent GMP fate-mapping tool, we propose an alternative model where GMPs give rise to cMoPs and proNeus (*purple path*, *Ms4a3*$^{TdT+}$) whereas MDPs give rise to Ly6C^{hi} monocyte-like cells independently of a progenitor intermediate. With evidence from other groups, we propose that MDPs instead give rise to the FLT3^{+} R2 monocyte population described by Menezes et al. (58), which is a MoDC-like cell–producing pool, whereas cMoPs give rise to Ym1^{+}Ly6C^{hi} monocytes, which were shown to have neutrophil-like features similar to ones described by the Goodridge group. We believe this revised model combines the various studies and evidence provided and helps create a framework for understanding myeloid cell ontogeny and function. Abbreviations: cDC, conventional DC; CDP, common DC progenitor; cMoP, common monocyte progenitor; CMP, common myeloid progenitor; DC, dendritic cell; GM-CSF, granulocyte-macrophage colony-stimulating factor; GMP, granulocyte-monocyte progenitor; iNOS, inducible nitric oxide synthase; LPS, lipopolysaccharide; MDP, monocyte and DC progenitor; MoDC, monocyte-derived DC; pDC, plasmacytoid DC; proNeu, proneutrophil; TpMo, transitional premonocyte.

are the primary progenitor of Ly6C^{hi} monocytes during homeostasis (56, 57). Supporting this, previous work from Sathe et al. (49) found no evidence for a common restricted MDP leading to both macrophages and Flt3-dependent resident DCs. Together, our studies prompt the notion that MDPs may not give rise to cMoPs and Ly6C^{hi} monocytes in steady state, but rather to cells with cDC features, challenging the relevance of the MDP population. More work is needed to fully decipher the nature of MDP-derived cells, and recent work in humans suggests that this lineage be might more related to the proinflammatory DC type 3 (DC3) lineage rather than the monocytic lineage (64–66).

Neutrophils, unlike monocytes, are solely derived from GMPs in adult hematopoiesis. Through high-dimensional single-cell analyses, we and other groups have characterized and traced the developmental trajectory of bone marrow neutrophils (15, 17, 18, 20, 21). Complications arise in reaching a common consensus regarding the identity of the neutrophil progenitor, as each group describes overlapping populations in terms of gene signatures and surface protein expression levels (3, 4, 19, 26, 28). Importantly, we showed that the earliest committed neutrophil progenitor (referred as proNeus) exists within the GMP population, further confirming the heterogeneity within the GMPs as previously suggested (17, 55). Of note, skewing of fate commitment between monocyte and neutrophil lineages was shown to be orchestrated by granulocyte colony-stimulating factor (G-CSF) during bacterial sepsis, reinforcing early studies demonstrating the use of growth factors to direct cell fate in myeloid progenitors (67). Monocyte fate can be similarly skewed, shown in listeria infection models and through direct influence of IFN-γ possibly produced by bone marrow natural killer cells (68–70).

Following the classical hierarchal view of hematopoiesis, GMPs appear as one of the last oligopotent progenitors to be formed, suggesting an evolutionary and strategic design to respond quickly to the growing inflammatory threats we face. Indeed, both monocytes and neutrophils seem to have appeared first in Osteichthyes (71, 72). Earlier invertebrate life-forms have specialized cells called hemocytes having features of both neutrophils and monocytes (73). Surprisingly, appearance of distinct neutrophils and monocytes coincided with the appearance of the adaptive immunity, suggesting intricate interplay and cross talk of these specialized myeloid cells and lymphoid cells that allow for a robust immune response. Unlike other progenitors, GMPs are highly active, providing constant replenishment of both major myeloid cell types. GMPs can modulate their own differentiation potential and subsequent cell output in response to stimulation. A study using immune spatial mapping of GMPs demonstrated that these progenitors are dispersed throughout the bone marrow under homeostatic conditions. Additionally, this study also revealed that GMP cluster formation is highly dynamic during emergency myelopoiesis (74). Thus, GMPs allow for agile and precise control of myeloid lineages throughout both homeostatic and pathological situations, resulting in the eventual regulated distribution of myeloid cell types seen in the bone marrow and circulation (74, 75). Taken together, these findings underline the importance of understanding the origins of GMP-derived cells and how they impact the underlying heterogeneity of myeloid cells in lymphoid organs and tissues.

SOURCES OF MYELOID HETEROGENEITY IN PERIPHERAL TISSUES

GMPs are found in both the bone marrow and spleen, and their local environment has a major impact on the eventual production of myeloid cells and progeny phenotype. Here, we describe how each distinct myeloid cell development site can influence GMP effector cell progenies through unique niche factors and neighboring cell types. This forms a foundation for delineating heterogeneity within the various peripheral tissues.

Bone Marrow

Myeloid cells are generated and stored in the bone marrow. The earliest development of myeloid cells in the bone marrow is detected at E17.5 by the seeding of definitive HSCs derived from the aorta-gonad-mesonephros and expanded in the fetal liver (76). Advanced imaging and single-cell sequencing confirm this, suggesting an initial bias toward neutrophil development at E18.5, possibly due to the lack of key stromal niche cells in the fetal marrow (77). These various stromal cell types provide the necessary lineage-instructive cues and growth factors for myeloid differentiation and maturation (78–80). Committed myeloid progenitors expand and generate a constant

supply, maintaining a reservoir of myeloid cells not only for mobilization to inflamed sites but also for certain expanding tissues (dermis and gut lamina propria are the most-studied examples) that relies on such postnatal monocytes to generate their pool of RTMs (8, 13). These specialized precursors follow discrete differentiation pathways outlined by an orchestrated action of various transcription factors. Studies have traced and defined each myeloid developmental intermediate, increasing our understanding of developmental dynamics, cell fate decision, and ontogeny (18, 47, 81–85).

Myeloid precursors can also exhibit unique functions besides expanding their respective myeloid pools. For example, McAlpine et al. (86) showed that the neutrophil precursor (preNeu) secretes macrophage colony-stimulating factor (M-CSF)/CSF-1 through hypocretin signaling to regulate monocytopoiesis. Their study further demonstrated that sleep deprivation causes unbalanced hypocretin signaling, leading to increased monocytopoiesis and atherosclerosis through M-CSF production by bone marrow preNeus. It is, then, speculative whether this function of a precursor extends to other myeloid precursor subsets and provides fine-tuning of hematopoiesis due to their localization with other hematopoietic cell types in the bone marrow. We have shown previously, through optically cleared marrow imaging, that preNeus tend to form clusters in the bone marrow and are tightly associated with CXCL12-expressing stromal cells. Perhaps this cluster formation allows concentrated and localized production of M-CSF for hematopoietic regulation (87). Similarly, clustering of GMPs in the bone marrow was shown to be important for regenerative hematopoiesis after myeloablative treatment, suggesting a functional aspect of their spatial distribution (74). Indeed, recent multiplex imaging of the bone marrow has further shown discrete localization of progenitors within the bone marrow niche and dynamic changes during stress or infection (88). It was observed that the various myeloid progenitors, though originating from a common progenitor, are distinctly localized, suggesting unique requirements for lineage-restricted development and maturation. Beyond spatial segregation of differentiation, it is interesting to speculate that such secretion of a key cytokine for monocyte differentiation (M-CSF) by neutrophil precursors may represent a form of regulatory cross talk between these two lineages arising from a common progenitor, the GMP. It will be interesting to further investigate whether such lineage-regulating cytokines are also produced in the various developmental states of monocytes and neutrophils.

During inflammation, early myeloid precursors and immature myeloid cells can also be found in the periphery, mobilized prematurely for effector functions. It is still unclear what they do in these circumstances, but recent studies have provided evidence of novel functions besides proliferative activity. Monocyte precursors, called transitional premonocytes, have been shown to perform similar effector functions as their mature counterparts while having a lower inflammatory profile and were important for replacing dying RTMs during bacterial infections when mature monocytes were susceptible to cellular death (89). Neutrophil precursors were also observed in the periphery, although their functions are yet to be elucidated. Hedrick's group reported that the frequencies of these precursors, called Neps, were associated with increased severity in melanoma patients and were immunosuppressive (21). Similarly, increased numbers of preNeus, which are thought to lead to the expansion of PD-L1^{+} dysfunctional neutrophils, were observed in patients with severe SARS-CoV-2 (90, 91).

Spleen

Development of myeloid cells is not constrained to the bone marrow but can occur at alternative sites of myelopoiesis such as the spleen and liver. Extramedullary hematopoiesis commonly occurs in the spleen. Although it does not provide significant hematopoietic activity, the spleen can adapt quickly in size and cellular output during inflammatory insults to provide a substantial

contribution of inflammatory myeloid cells (92). Hematopoietic stem and progenitor cells (HSPCs), developing in the spleen, are suggested to have a myeloid bias, possibly due to a lack of IL-7, which is required for B cell development in the red pulp (93). Seeded by mobilized HSPCs from the bone marrow, they are retained in the spleen through VCAM-1^+ macrophages (94). Engrafted in their specialized niches in the red pulp, HSPCs expand and differentiate, tightly regulated by factors such as neuronal activation and Tlx1-expressing mesenchymal cells (95, 96).

These myeloid cells developed in situ in the spleen have been shown to possess differential functions compared to their bone marrow counterparts, due to factors provided by the distinct niches they develop in (97–99). In cancer, myeloid cells generated from the spleen are thought to acquire T cell–suppressive functions and increased inflammatory cytokine production (100). Splenic HSPCs from tumor-bearing mice were shown to be reprogrammed into these suppressor cells through endogenous GM-CSF production by HSPCs (101). In a follow-up study, the same group further indicated that this process depends on PKR-like ER kinase pathways (102). Swirski et al. (103) showed that the spleen is a large reservoir of monocytes that differentially respond to myocardial injury. These splenic monocytes were shown to be specifically recruited to the lesions for their effector functions, like wound healing, or after lung inflammation (104, 105).

With respect to neutrophils, Deniset et al. (106) demonstrated that clearance of *Streptococcus pneumoniae* infection was significantly attributable to mature Ly6G^{hi} resident neutrophils in the red pulp of the spleen. These neutrophils were also shown to induce immunoglobulin class switching and antibody production of marginal zone B cells by secreting factors such as BAFF, APRIL, and IL-21 (107). Moreover, neutrophils in the perifollicular regions have been reported to enhance B cell responses to canonical T cell–independent antigens such as those from *S. pneumoniae* (108). These marginal zone neutrophils, also named N_{BH} cells, were shown to specifically acquire B cell helper properties only in the steady state (107, 109, 110). Notably, one study showed that these perifollicular neutrophils can preferentially localize in the red pulp through IL-18, suggesting that inflammation can dictate their localization and function (111). Thus, the spleen is both a developmental site of myelopoiesis and a peripheral tissue for distinct myeloid cell types to elicit innate and humoral immune functions.

Circulation

Among the various circulating blood cells, neutrophils and monocytes account for just 20–30% and ~4%, respectively, in mice. Notably, a large fraction of these myeloid cells exist as a pool of marginated cells retained in the lung vasculature. Upon stimulation through mediators such as corticosteroids and G-CSF, neutrophils can be quickly mobilized into the periphery to perform their effector functions (112, 113). However, neutrophils mobilized through corticosteroids are likely to have altered functions, with reduced migration and activation toward inflammatory sites (114). Similarly, mobilization with G-CSF has been shown to downregulate CXCL2-mediated chemotactic signaling, suggesting a regulatory mechanism of neutrophil numbers in circulation (115).

Once released into the circulation, neutrophils follow an intrinsic circadian aging program, governed by CXCR4 and Bmal1 (116, 117). As neutrophils age, they shed CD62L while increasing their expression of CXCR4, which is required for homing to tissues where they are cleared (117). This process of neutrophil aging was reported to be regulated by the microbiome, through TLR- and MyD88 (myeloid differentiation factor 88)-mediated signaling pathways (118). Fresh neutrophils were shown to be proficient in cell extravasation and infiltration, while aged neutrophils showed increased protection against fungal infections. However, these aged cells were also shown to be detrimental to vascular injury in a model of ischemic reperfusion (116). This points to a spectrum of neutrophil ages and functions in the circulation, with implications for

their infiltration and acquisition of tissue-specific signatures. Moreover, as the human circulation consists of >50% neutrophils, it is likely this effect is only further magnified in human diseases.

For a long time, monocytes were thought to be the precursors of RTMs, and their sole purpose to replenish their numbers (119, 120). While fate-mapping studies have shown this to be untrue, monocytes do play significant roles in replacing the macrophage pool in specific tissues and inflammatory conditions (6, 8). Two subsets of monocytes can be found in the blood: classical Ly6C^{hi} monocytes, which are CX3CR1^{lo}CD43^{-}, and patrolling Ly6C^{lo} monocytes, which are CX3CR1^{hi}CD43^{+} (121, 122). These subsets are short-lived cells with half-lives of about 20 h (Ly6C^{hi} monocytes) and 2.2 days (Ly6C^{lo} monocytes) (122). While in the circulation, Ly6C^{hi} monocytes progressively lose Ly6C expression and give rise to Ly6C^{lo} patrolling monocytes that survey the vascular endothelium under the control of transcription factor *Nr4a1* (46, 122, 123). Also known as macrophages in the circulation, Ly6C^{lo} monocytes scavenge for microparticles along the endothelium and direct neutrophils to kill injured endothelial cells in a TLR7-dependent manner (124). Moreover, they are also involved in tissue repair in the myocardium (125, 126). Ly6C^{hi} monocytes also infiltrate into tissues in the steady state, giving rise to RTMs in certain tissues. In inflammation, the recruitment of monocytes is dramatically enhanced, giving rise to inflammatory cells undergoing monocyte-to-phagocyte transition with features of both macrophages and DCs, which are often the same cells with different names (127). Although Ly6C^{lo} monocytes were thought to be unable to differentiate into macrophages, recent studies have provided evidence of Ly6C^{lo} monocyte-derived macrophages with unique functions (128, 129). Hoffman et al. (128) demonstrated the generation of CD9^{+} macrophages that provided an intracellular replication niche by detoxifying oxidized lipids for use by invading salmonella bacteria. Perhaps differentiation of Ly6C^{lo} monocytes is restricted to certain conditions and specific inflammatory cues are required to enable this process.

Although it is generally assumed that most circulating leukocytes are terminally differentiated cells, HSPCs are detected in the circulation under physiological conditions (130, 131). Massberg et al. (132) demonstrated that despite their very low frequencies (~0.01%), HSPCs could enter the bloodstream, traffic to peripheral tissues, and return to the bloodstream via lymphatics. In addition, our studies also revealed that inflammation is accompanied by increased mobilization of immature myeloid cells, such as immature neutrophils and transitional premonocytes (87, 133). It is likely that this mobilization also occurs under homeostatic conditions but is intensified during inflammation. Conceivably, the immune system might utilize the circulatory system to regulate the mobilization of myeloid precursors from the bone marrow to ensure that an adequate number of myeloid cells are present at extramedullary sites to perform their functions. Intriguingly, a recent study revealed that myeloid progenitors, but not other progenitors or hematopoietic stem cells, can be mobilized directly from the bone marrow to target tissues via the lymphatic circulatory system during systemic inflammation (134). It is still unclear how this premature release of myeloid precursors into the circulation affects further heterogeneity and function as they arrive at the various peripheral inflamed tissues.

CONTRIBUTION OF GMP-DERIVED PHAGOCYTES IN TISSUE MYELOID CELL DIVERSITY

During homeostatic conditions, the dominating myeloid cells in tissues are the long-lived macrophages. They reside in almost all organs to maintain tissue homeostasis. They colonize organs at the very early stages of embryonic development to support organogenesis (135) and subsequently support tissue function. Long-lived macrophages clear their surroundings by phagocytosing cellular materials, regulate tissue repair and maintenance, preserve tissue integrity, and

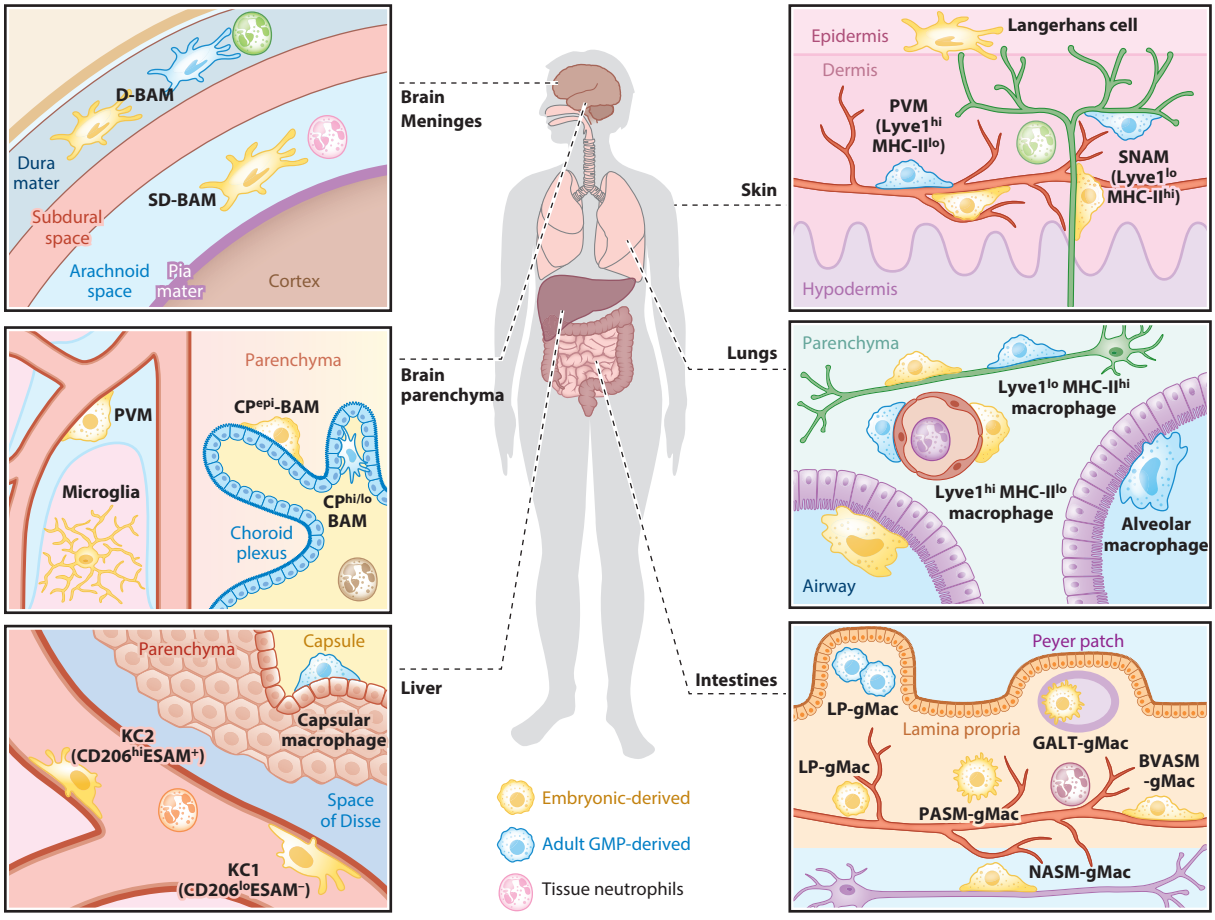

Figure 3

Contribution of GMP-derived cells in tissue myeloid diversity. RTMs make up a large proportion of tissue myeloid cells. Specific macrophage populations are continuously replaced by circulating monocytes that adopt RTM identity based on local niche signals. Neutrophils continuously perform immunosurveillance in tissues and similarly adopt tissue-specific functions distinct from those among the circulating pool. Each subtissular region contributes to the functional heterogeneity of myeloid cells. Abbreviations: BAM, border-associated macrophage; BVASM, blood vessel–associated self-maintaining; CP^{epi}-BAM, epiplexus macrophage; $CP^{hi/lo}$ BAM, choroid plexus macrophage; D-BAM, dural BAM; ESAM, endothelial cell–selective adhesion molecule; GALT, gut-associated lymphoid tissue; gMac, gut macrophage; GMP, granulocyte-monocyte progenitor; KC1, Kupffer cell 1; LP, lamina propria; NASM, nerve-associated self-maintaining; PASM, Paneth cell–associated self-maintaining; PVM, perivascular macrophage; RTM, resident tissue macrophage; SD-BAM, subdural BAM; SNAM, sensory nerve–associated macrophage.

mount the first-line defense against pathogens (136). Despite their common origin, they depend differentially on circulating monocytes for their renewal (7). Unlike monocytes, which are short-lived and are continuously replaced, macrophages can self-renew independently of bone marrow hematopoiesis for prolonged periods of time, potentially throughout the life of the organism (6). Depending on the tissue in which they reside, macrophages express distinct phenotypes (137–139). The identity of macrophages depends on several factors: tissue environment, time, origin, and transcription factors (140). These phenotypic differences underlie the various specialized functions of macrophages (**Figure 3**): for example, regulating pigmentation in zebrafish skin (141), maintaining a tattoo in the skin (142), removing surfactant in the lung (143), recycling iron from

senescent red blood cells in the spleen (144), fostering spermatogonial differentiation in the testis (145), and wiring neurons in the developing brain (146).

Although short-lived, neutrophils infiltrate and reside in healthy tissues for periods of time (147, 148). Unlike macrophages that reside in tissues for long periods of time, neutrophils are instead constantly replenished by waves of freshly developed neutrophils circulating into tissues to maintain tissue surveillance (117). Tracing the life span of these neutrophils using Ly6G-restricted tamoxifen labeling suggests a modest range of 10–18 h (24). Like RTMs, neutrophils can also rapidly adopt tissue-specific signatures linked to specialized functions for tissue homeostasis (24). Although this concept in neutrophils is only beginning to be explored, it is likely that new studies will reveal the diversity of neutrophil function acquired through tissue imprinting. In this section, we consolidate the current evidence of tissue myeloid heterogeneity and its impact on both health and disease.

Lung

The lung is constantly exposed to environmental threats. Inhaled microbes and toxic particles must be neutralized without disrupting the essential gaseous exchange within the alveoli. Alveolar macrophages are the main tissue myeloid cell type and are involved in various functions to maintain surfactant levels, clearing foreign pathogens, and performing immune homeostasis (149–151). Alveolar macrophages are also capable of preserving their pool of embryonically derived cells during homeostasis. However, unlike brain-resident microglia, tissue-infiltrating monocytes make up an increasing proportion of alveolar macrophages over time (57). This replacement was shown to provide beneficial protective roles during infections. It has been shown that a gammaherpesvirus infection induced a recruitment of monocyte-derived alveolar macrophages that were able to inhibit the development of allergic asthma (152). Supporting this, a recent study demonstrated that mice recovered from a previous influenza infection were better protected against a bacterial *S. pneumoniae* infection. This was primarily attributed to monocyte-derived alveolar macrophages, which displayed distinct transcriptomic and functional profiles (149). Self-sustaining, embryo-derived alveolar macrophages were also shown to acquire similar memory-like augmentations. Yao et al. (153) demonstrated that an acute adenoviral infection induced a memory alveolar macrophage phenotype with increased MHC-II expression. These memory alveolar macrophages were able to confer protection against *S. pneumoniae* through enhanced neutrophil recruitment.

Besides alveolar macrophages, lung RTMs are also made up of interstitial macrophages devoid of SiglecF expression. They exist in the parenchyma of the lung tissue, where they provide homeostatic functions such as immune regulation (105). Recent fate-mapping studies revealed that these tissue macrophages exist as two separate lineages and localize differentially within the interstitial space (154). Specifically, Lyve1^{+}MHC-II^{-}CX3CR1^{-} interstitial macrophages can be found preferentially near blood vessels, while Lyve1^{-}MHC-II^{+}CX3CR1^{+} macrophages are localized near nerve bundles and endings. Interestingly, this dichotomy of macrophage subsets is consistent in other organs and tissues like the heart, fat, and skin of mice and humans (154–156). Functionally, Lyve1^{-}MHC-II^{+}CX3CR1^{+} macrophages have enhanced antigen presentation, while Lyve1^{+}MHC-II^{-}CX3CR1^{-} interstitial macrophages limit tissue fibrosis and regulate cell recruitment into the lung with high levels of IL-10. Therefore, as exemplified in the lung, the specific local tissue environment plays a major role in shaping the heterogeneity of myeloid cells in tissues.

Besides macrophages, neutrophils and monocytes exist mainly in the intravascular space, forming a marginated pool of myeloid cells transiting through the thin-walled vasculature of the lung (157–159). These myeloid cells have adjusted their morphology to squeeze through the capillaries of the alveoli (160). Interestingly, this localization of neutrophils and monocytes enables them to

behave as a reservoir of myeloid cells that can quickly mobilize in response to inflammatory cues. This behavior was shown to be mediated by the chemokine CXCL12 and its receptor CXCR4. Inhibition of CXCR4 results in the release of marginated neutrophils and monocytes from the lung to sites of injury (113, 133). Endotoxins like LPS activate these cells for bacterial clearance, inducing rapid crawling in the pulmonary endothelium (133, 161). In steady-state lungs, marginated neutrophils are regulated by circadian oscillations, retaining the most in the lung tissue at night (147). Furthermore, aged neutrophils ($CD11b^{hi}$L-$selectin^{lo}CXCR4^{+}$) constitute the predominant population in the lung (162). An earlier study suggested that the aging of neutrophils in circulation is essential for these cells to initiate their effector functions (163). However, a recent study demonstrated that neutrophil aging is diurnally regulated to promote effective antibacterial functions and avoid undesirable vascular damage (116). In addition, due to their localization, neutrophils rapidly acquire a lung-specific signature and acquire proangiogenic characteristics that may contribute to the integrity of the lung vasculature. Further research should investigate how this reprogramming influences tissue homeostasis and disease progression (24).

Liver

Macrophages are the most abundant immune cell type in the liver, comprising two main populations: Kupffer cells (KCs) and liver capsular macrophages (LCMs). Karl Wilhelm von Kupffer discovered KCs as stellate cells residing in the nonparenchyma liver and mistakenly described them as endothelial cells (164). Specifically, they localize along the sinusoidal endothelium in direct contact with blood, acting as important scavengers that clear pathogens and remove damaged erythrocytes from the blood (165). Recent multiplex imaging further showed their asymmetric distribution near periportal regions, driven by the commensal bacteria entering the liver (166). These cells express canonical macrophage markers CD64, F4/80, and CD11b, and also specific markers such as Clec4F (C-type lectin domain family 4 member F) and Tim-4, representing the dominant macrophage population in the liver (167).

Like other RTMs, KCs were previously thought to be derived from circulating monocytes, but fate-mapping models and parabiosis studies have shown that KCs are long-lived, self-maintaining cells derived from embryonic precursors (6, 29, 35). Although in direct contact with blood, circulating monocytes do not contribute to KC numbers at the steady state. However, selective depletion of KCs allowed for their replacement with $Ly6C^{hi}$ monocytes that sequentially adopt a KC phenotype akin to the resident population (167). Both hepatic stellate cells and endothelial cells collectively promote monocyte differentiation into KCs, regulated by transcription factors ID3 (inhibitor of DNA 3) and LXR-α (liver X receptor α) (168). LXR-α, specifically, is controlled by the transcription factor ZEB2, which also governs RTM identity in other organs (169). Sakai et al. (170) further revealed that the liver-derived Notch ligand DLL4 and TGF-β are critical for KC identity determination. These studies collectively emphasize that local niches are key regulators of reprogramming myeloid cell identity. However, there are ontogenetically based differences among KCs. One study noted some functional differences between resident KCs and monocyte-derived KCs (MoKCs), including the uptake of bacterial pathogens (171). This mirrors observations of lung alveolar macrophages, hinting at a common feature of monocyte-derived KCs and their functional implications during inflammation (172). Similarly, a study demonstrated that the influx of monocyte-derived KCs, through diet-induced inflammation, replaced the tolerogenic resident KCs, which led to increased severity of liver disease (173, 174). In addition, Remmerie et al. (175) identified a subset of these recruited macrophages that resembled previously documented adipose tissue macrophages (176). These lipid-associated macrophages, distinct from KCs, correlate with increased disease severity and fibrosis. However, it is yet unclear whether these recruited macrophages play a direct role in pathogenesis, as monocyte-derived KCs have

been shown to also be important in the resolution phase of acute liver injury, suggesting that their presence can be beneficial (177).

With limited markers for flow cytometric analysis, KCs were thought to be homogeneous. However, the advancements in high-dimensional analyses allowed us to characterize the heterogeneity of KCs (178). Recently, two distinct KC populations were identified with differential expression of the scavenger receptor CD206 and endothelial cell–selective adhesion molecule (ESAM): KC1s and KC2s (179, 180). $CD206^+ESAM^+$ KC2s possessed unique metabolic functions, and their selective depletion prevented diet-induced obesity (179). In addition, KC2s are more responsive to IL-2 compared to KC1s and are thus able to cross present viral antigens effectively to $CD8^+$ T cells in a murine model of hepatitis infection (180). Similar heterogeneity can also be observed in human livers, suggesting a conserved heterogeneity important for homeostatic function (181).

Unlike KCs that reside in the sinusoidal space, liver capsular macrophages form a contiguous network in the surface of liver capsule (182). These cells are identified as $CD64^+F4/80^+$ but do not express canonical KC makers such as Tim-4 or Clec4F. Instead, they express high levels of DC markers MHC-II and CD11c, evidence from early studies used to suggest they were not macrophages (173, 178, 183). Moreover, these $CX3CR1^+$ cells have dendritic morphologies, enhancing their ability to sense bacteria and other microbial products to prevent their further dissemination from the peritoneum (182). These macrophages, unlike KCs, are constantly replaced by circulating monocytes, similar to the constant replenishment seen in colonic macrophages (8). Notably, a recent study demonstrated an alternative source of liver tissue macrophages during inflammation. Wang & Kubes (184) showed that $GATA6^+$ peritoneal cavity macrophages could rapidly invade the liver during sterile injury through a nonvascular route and across the mesothelium and into the injured liver parenchyma. In their study, the depletion of these cavity macrophages was lethal during CCl_4-induced acute liver injury, suggesting their essential contributions during wound healing. A recent dual-recombinase-mediated fate-mapping model for cavity macrophages disputes these findings (185). Imaging of the $CD45^+GATA6^+$-labeled cavity macrophages revealed that although these macrophages do infiltrate the liver as described previously, they do not penetrate deep into the liver parenchyma. Moreover, selective depletion of these macrophages did not significantly impact tissue repair, and the majority of the $GATA6^+$ macrophages in CCl_4-treated livers were instead KCs (185). These findings warrant further investigation and the use of other disease models to elucidate the contribution of cavity macrophages to local tissue macrophage heterogeneity and function. We hypothesize that the depletion of cavity macrophages through intraperitoneal injections of liposomes induced cell death of an uncharacterized subset of macrophages that is responsible for the phenotype observed by Wang & Kubes (184). As shown by Jin et al. (185), liposome-induced depletion comparatively showed higher levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and tissue fibrosis. These indicate that the treated livers from each group may have varying levels of inflammation, which inadvertently caused a disparity in the observations made.

Similarly in the lung, liver-resident neutrophils mainly localize in the intravascular space (147). Neutrophil retention in the liver, unlike many tissues elsewhere, is not temporally controlled, suggesting an influx of both fresh and aged cells into the liver sinusoids. Using a laser-injury model, these neutrophils were observed to crawl through the sinusoids toward the focal injury within 2 h (186). After their contribution to tissue repair and debris clearing, they were expected to die and be cleared by surrounding macrophages (187). However, Wang et al. (187) observed that these liver neutrophils reverse-transmigrated out of the injury site and back into the circulation. We speculate that this phenomenon can be contributed by signals from the local tissue environment and surrounding niche cell types. Further studies should investigate whether this behavior also

occurs in other tissues or whether the liver imprints a tissue-specific function of liver-reparative neutrophils.

Skin

Among the various tissues, RTMs in skin tissue were the first studied to have a non-monocyte origin. Parabiosis experiments showed that Langerhans cells (LCs), initially considered as epidermal DCs, are self-maintaining, without contribution from circulating blood precursors (188). With the help of fate-mapping tools, investigators then came to understand that LCs are macrophages by ontogeny and are mostly derived from fetal liver monocyte precursors with minor contributions from yolk sac progenitors (10, 189). Yolk sac–derived primitive macrophages could be detected in the embryonic skin between E10.5 and E13.5 and were shown to persist throughout adulthood (10). Hoeffel et al. (29) subsequently used *Csf1*$^{Cre/EYFP}$ and *Runx1*$^{Cre/EYFP}$ fate-mapping models and demonstrated the replacement of yolk sac–derived macrophages by fetal liver monocytes during late embryogenesis. LCs are unique tissue macrophages with DC functions such as migrating toward lymph nodes and presenting antigens to T cells (190, 191). As initially shown, depletion of LCs with UV exposure led to replacement by circulating monocytes through CCR2 signaling (192). This follows a similar finding with KCs, where available niches created by depletion allow for engraftment of monocytes (7).

Aside from LCs, two subsets of dermal macrophages have also been characterized, distinguished by MHC-II expression (13, 154, 193). Dermal macrophages were shown to have a dual origin of both fetus- and adult-derived monocytes, which was later confirmed with fate-mapping experiments (57, 194). Like interstitial macrophages in the lungs, Lyve1^{-}MHC-II^{+}CX3CR1^{hi} dermal macrophages localize close to peripheral nerves (154) and contribute to myelin degradation and nerve regeneration (194). These macrophages are also known as sensory nerve–associated macrophages. Kolter et al. (194) demonstrated that these long-lived macrophages contribute to axon sprouting at lesioned nerves during nerve injury. Injury to the skin similarly recruits inflammatory monocytes that differentiate into macrophages indicated by a "monocyte waterfall" phenotype (195). Importantly, although both subsets of dermal macrophages can be replenished by monocytes during injury, the residential CX3CR1^{lo} interstitial macrophages can also self-maintain skin macrophage numbers as indicated previously (196, 197). Although sensory nerve–associated macrophages are of a dual origin, local niche signals provide definitive instructional cues for their cell fate identity of self-maintaining resident macrophages.

Neutrophils in skin acquire functions associated with epithelial and connective tissue growth (24). These skin-resident neutrophils are quick to respond to sterile injuries and microbial infections, forming swarms around the injury or infected site (2, 198). Cell death of these early skin neutrophils leads to further recruitment of neutrophils either from distant regions of the skin or from the circulating pool (2). Comparative sequencing of skin neutrophils revealed tissue imprinting of functions associated with epithelial and connective tissue growth, suggesting their enhanced capabilities for wound healing (24). Neutrophils are capable of self-limiting their swarming, possibly due to imprinting by tissue-specific signatures (199). Furthermore, local tissue macrophages can cloak microlesions to prevent excessive neutrophil recruitment (200). Uderhardt et al. (200) demonstrated that neutrophils were unable to swarm at microlesions, as they failed to detect the necessary alarmins required for neutrophil activation. Failure to cloak, in the case of larger lesions, instead led to the neutrophil-dependent recruitment of monocytes required for tissue repair (200, 201). These recruited monocytes, besides differentiating into reparative macrophages, were recently shown to regulate leptin-dependent vascularization and wound healing through secretion of endogenous ghrelin (202). Thus, these findings indicate that several regulatory mechanisms exist to prevent overt neutrophil-driven inflammatory responses at this barrier site.

Brain

Perhaps the most complex heterogeneity in tissue macrophages exists within the central nervous system (CNS). The brain comprises various subtissue compartments involved in specific aspects of brain physiology and function (203). Such a complex organ requires an intricate interplay between immune, stromal, and neuronal cell types within each specific niche. Two categories of macrophages exist in the brain: microglia and border-associated macrophages (BAMs) (204–206). Microglia reside in the parenchyma, whereas BAMs reside in specific regions such as the meninges, blood vessels, and choroid plexus (205, 207–209). Cortex-associated microglia require CSF-1R signaling, but not CSF-1, for survival, and depletion of CSF-1R demonstrated the local repopulating ability of microglia progenitors residing locally in the brain (9, 210, 211). Depletion also indicated that these macrophages do not play significant roles in cognitive ability and function, whereas some have reported otherwise (212, 213). IL-34 shares the same receptor, CSF-1R, and is also involved microglia development, specifically in the early postnatal brain (214, 215). Recent reports revealed that specific depletion of CSF-1 or IL-34 leads to severe depletion of microglia in discrete anatomical regions of the brain, suggesting a niche-dependent control of microglia development for cognitive and motor function (214, 216). Although microglia were presumed to be derived from circulating monocytes, fate-mapping studies have shown that they are derived from the yolk sac progenitors independent of *Myb* (9, 12, 217). Moreover, partial depletion of microglia can allow peripherally derived macrophages to engraft and become microglia featuring a unique transcriptome distinct from that of resident microglia (218).

Like microglia, BAMs are derived from yolk sac progenitors, although the complete ontogeny of each BAM subset is still being debated (219–221). For example, choroid plexus macrophages have comparatively shorter life spans and are renewed partially by $CCR2^{+}$ circulating monocytes (219). Also, a recent study utilized the $Ms4a3^{Cre}Rosa^{TdT}$ GMP fate-mapping model and demonstrated that meningeal $CD206^{+}MHC\text{-}II^{+}$ macrophages were progressively replaced by monocytes, at a higher rate than perivascular macrophages (222). This is in line with a previous work (209). High-dimensional gene and protein expression analyses have revealed an incredible assortment of macrophage identities, and their individual functions are just starting to be determined (205, 209, 222).

Notably, recent reports propose that this supply of myeloid cells into the CNS is locally provided by nearby cranial and vertebral marrow niches through direct channels (223–226). These studies shed light on the recruitment route of myeloid cells into the meninges and potential skull marrow–specific priming of myeloid cells in response to viral or bacterial infections in the CNS (225–227). Interestingly, this mirrors a recent study demonstrating that neutrophils and monocytes are present in healthy gingival tissues and that these cells derive from the gingival HSPCs, which have the same differentiation capacity as their counterparts in the bone marrow (228). Regarding resident neutrophils of the brain, these cells have been detected through these studies, and signs of compartment-specific neutrophils can already be observed, similar to the various BAMs (209). This, together with new insights of CNS-specific skull marrow supply, paves the way to future studies investigating novel functions in their involvement in immunosurveillance, brain function, and disease pathogenesis.

Gut

The gut is a highly complex system of organs comprising specialized tissue types that constantly encounter foreign antigens during digestion and nutrient absorption. As such, the immune compartment in the mucosa is likely the largest, comprising a tightly woven mesentery and lymphatic system for the migration of various effector cells (229). Myeloid cells, mainly macrophages,

reside throughout the gut, providing essential functions for antigenic tolerance and protection. In the distal colon, $CD11c^{hi}$ gut macrophages can have balloon-like protrusions that are inserted between epithelial cells, preventing fungal toxin absorption by nearby epithelial cells by rapidly sampling these metabolites (230). Gut macrophages can also enable antigenic tolerance by sampling food and bacterial antigens from the intestinal lumen through transepithelial dendrites, transferring antigens to resident DCs within the lamina propria and Peyer patches (231, 232). These macrophages within the mucosa are the largest population of immune cells in the gut and are constantly renewed by recruited monocytes, perhaps through their constant antigenic exposure or influences by the microbiota (8, 233). However, recent studies showed that some macrophages in the submucosa and muscularis layer are long-lived and do not require replacement by monocytes. These self-maintaining $Tim\text{-}4^{-}CD4^{+}$ and $Tim\text{-}4^{+}CD4^{+}$ macrophages are localized specifically near enteric neurons, blood vessels, Peyer patches, and the muscularis externa (234, 235). Like BAMs in the brain, macrophages in each subanatomical niche acquire specialized functions influenced by their local environment. For example, macrophages near enteric neurons (called NASM-*g*Macs) were shown to control neuron-evoked secretion, neurogenic contractility, and intestinal transit (234). Neutrophils in the gut are not homogeneously distributed but cluster in discrete innate lymphoid follicles, surrounded by CD169-expressing macrophages (147). It is postulated that the infiltration of these neutrophils suppresses IL-23 production in the macrophages, which regulates IL-17-producing T cells. This in turn regulates G-CSF levels (147). Therefore, these studies demonstrate the multiple facets of myeloid cells in the gut, and future specific depletion models will be required to further reveal both the homeostatic and inflammatory functions of each unique myeloid phagocyte.

MYELOID CELL REPROGRAMMING IN DISEASE STATES

To this point, we have primarily discussed how distinct cellular sources may contribute to the heterogeneity of peripheral and tissue-resident myeloid cells mostly under homeostatic conditions. It is essential to highlight that the differential involvement of peripheral and resident myeloid cells, in various inflammatory and disease states, is challenging to examine. Therefore, we believe that a thorough understanding of ontogeny could provide a framework for understanding the specific anatomical sites and temporal sequence of the formation of the distinct myeloid cells and their functional roles during disease states. At the steady state, GMP-derived myeloid cells steadily infiltrate tissues and acquire tissue-specific activities in response to environmental cues. The situation is considerably more complicated during inflammatory or disease states, as specific inflammatory stimuli can regulate and shape myeloid cell function locally but also through developmental changes when the bone marrow senses the challenge, which contribute to disease progression and resolution.

The intensity of systemic inflammatory stimuli is known to affect myelopoiesis by influencing cell fate decisions and production. It is well established that increased myeloid production in the bone marrow or spleen is associated with numerous illnesses, including obesity, atherosclerosis, sepsis, and malignancy (87, 236–239). This phenomenon is attributable to proinflammatory cytokines such as IL-1β, which directly increase cell division and skew HSC differentiation toward myelopoiesis (240). In addition, other molecules such as TLR4, GM-CSF, and IFN-γ can increase myeloid cell production in a similar manner (75). While myelopoiesis proliferative activity in bone marrow can be rapidly increased in response to systemic stimuli to supply sufficient myeloid effector cells, specialized sites such as gingival tissue, the skull, and vertebral bone marrow can generate neutrophils and monocytes locally without relying on recruited cells. Systemic inflammatory signals can also greatly influence myeloid cell maturation and function.

For example, in a mouse model of lung adenocarcinoma, Engblom et al. (241) identified a tumor-promoting SiglecF^{hi} neutrophil subset derived from the bone marrow that they suggested was induced through RAGE (receptor for advanced glycation end products) signaling on osteoblast cells (242). In a recent study, Long et al. (243) demonstrated that systemic influences from the tumor, such as GM-CSF, can also induce transdifferentiation of erythrocyte progenitors into myeloid effector cells. This reprogramming of these cells enriched immunosuppressive functions and increased immune checkpoint inhibition resistance in patients.

Inflammation mobilizes immature myeloid precursors and cells into the bloodstream, and these circulating cells can be recruited into the tissues, thereby further contributing to myeloid cell heterogeneity in tissues. Immature bone marrow Ly6G^{+}CD101^{-} neutrophils are mobilized into the circulation, although their precise function remains unknown (87). Significantly, neutrophil precursors were identified in patients with severe SARS-CoV-2 infections (90, 91, 244, 245). A recent study indicates that dexamethasone treatment can regulate immature neutrophil activity in COVID-19 patients, increasing their numbers and enhancing their immunosuppressive properties relative to those in untreated patients (246). Conversely, circulating monocytes lose HLA-DR expression, indicating a monocytic myeloid-derived suppressor cell (MDSC)-like phenotype and impaired immunological function in COVID-19 patients. Moreover, lung-infiltrating monocytes acquire a ficolin-M signature while differentiating into a CD163/LGMN-macrophage population with a profibrotic signature, demonstrating the importance of tissue reprogramming in the generation of disease-specific myeloid cells (247–249). How myeloid cells are reprogrammed in diseased tissues is most likely best studied in tumors, where tumor-associated macrophages and neutrophils are transformed into protumor mediators of cancer growth under the influence of the local tumor microenvironment (250–253).

Together, these studies underpin the complex modes of myeloid cell reprogramming during inflammation, which involves a dynamic interaction between local and system-wide cues for myeloid cell generation and cell function modification. Based on this framework, we believe it will be possible to better understand heterogeneity of tissue myeloid cells in pathological states, providing new perspectives for therapeutic interventions.

CONCLUDING REMARKS

In recent years, multi-omics approaches and fate-mapping models have helped to improve our understanding of myeloid ontogeny. Although this knowledge has established the framework for characterizing myeloid cell heterogeneity in the resting state, understanding this heterogeneity in inflammation and disease states remains challenging. This complexity stems from their dynamic interactions with local and systemic stimuli, compounded by rapidly shifting transcriptional profiles and lack of surface markers for delineating subsets. Moving forward, the use of transcriptomic trajectory analyses, animal models allowing for time-stamping or bar coding for cell tracing, multiplex phenotyping techniques, and spatial transcriptomics will enable an enhanced view of myeloid cell development and differentiation. These techniques will reveal the intricate spatiotemporal kinetics of resident and recruited myeloid cells, aiding in the identification of key gene and protein signatures of myeloid cells transitioning between resting and challenged states and thus providing a new road map for understanding myeloid cell heterogeneity in disease settings.

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