MYELOID CELLS

Monocytes and their doppelgängers: An immunological crossroads

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Identity confusion has emerged in the field of monocyte research with the identification of monocyte-like "doppelgänger" populations that exhibit phenotypical traits of classical monocytes but seem to vary in their origin, function, or migration behavior.

In Fyodor Dostoevsky's *The Double: A Petersburg Poem*, the protagonist, Yakov Golyadkin, is portrayed as an antisocial, paranoid individual who encounters his doppelgänger—an exact physical replica of himself but with a radically different personality. Initially, their actions appear to complement each other, but, eventually, the doppelgänger seamlessly integrates into and appropriates Golyadkin's life. This unsettling development raises the question of whether Golyadkin and his double are separate entities or whether the doppelgänger is a manifestation of Golyadkin's own psychological breakdown. This motif of identity confusion extends beyond literature into the scientific realm. Scientists are rapidly identifying and naming new cell populations using single-cell technologies and fate-mapping models, often leading to ambiguity in cell identification. However, it is crucial to thoroughly understand both the origin and function of newly described cell subsets and to carefully evaluate their nomenclature. This issue has recently emerged in the field of monocyte research with the identification of monocyte-like "doppelgänger" populations that exhibit phenotypical traits of classical monocytes but seem to vary in their origin, function, or migration behavior. This raises the following questions: Are all of these populations actually monocytes, and do they really represent distinct subsets (Fig. 1A)?

Monocytes form the circulating component of the mononuclear phagocyte system (MPS), which also includes tissue-resident macrophages and FLT3 ligand (FLT3L)–dependent, *Zbtb46*-expressing conventional dendritic cells (cDCs). A distinguishing feature of monocytes is their ability to rapidly migrate into inflamed tissues in large quantities, where they act as a versatile "emergency squad." This dynamic response allows monocytes to adopt either a proinflammatory or regulatory phenotype, influenced, in part, by environmental and spatial cues, to help return the tissue to homeostasis (*1*). Compared with cDCs, the development and survival of monocyte-derived cells depend on signaling through the colony-stimulating factor 1 receptor (CSF1R).

Monocytes were considered to arise from monocyte/DC progenitors (MDPs), identified among granulocyte and macrophage progenitors (GMPs), which have lost their potential to generate granulocytes. MDPs subsequently differentiate into unipotent common DC progenitors (CDPs) or common monocyte progenitors (cMoPs), the latter of which give rise to classical monocytes (*1*). These classical monocytes, defined as Ly6C^{Hi} MHCII^{-} monocytes, enter the bloodstream and develop into nonclassical Ly6C^{Low} monocytes or, alternatively, leave the circulation, destined to become monocyte-derived tissue macrophages (*1*). However, this model, with MDPs as the exclusive monocytic precursor population and a homogenous classical monocyte population at its center, was recently challenged by the discovery of several doppelgänger cell populations within classical monocytes and revealed a dual origin of these cells.

MONOCYTE HETEROGENEITY AND DOPPELGÄNGERS

More than a decade ago, heterogeneity among classical monocytes was described by identifying Ly6C^{+} MHCII^{+} cells in the circulation (*2*). These cells were incorporated in the Immunological Genome Project, and, in contrast to conventional Ly6C^{Hi} monocytes, MHCII^{+} cells were characterized by *Cd209a* and *Cd74* expression. Unbiased single-cell RNA sequencing (scRNA-seq) of blood monocytes (CD11b^{+} CD115^{+}) reinforced the notion of monocyte heterogeneity. In addition to classical and nonclassical monocytes that were connected by an intermediate cluster of cells, the presence of a fourth *Cd209a*$^{+}$ population was evident (Fig. 1B) (*3*).

Although scRNA-seq has advanced our understanding of monocyte heterogeneity, it does not address ontogeny. A landmark study revealed that monocytes may, in fact, develop through two distinct pathways, the GMP and MDP routes, leading to a heterogeneous pool of cells that resemble classical monocytes from different origins (*4*). GMP-derived cells exhibit a gene expression pattern reminiscent of their granulocyte precursors (including typical neutrophilic genes such as *Elane*, *Prtn3*, and *Ctsg*) and are named neutro-like monocytes. In contrast, MDP-derived cells that express MHCII-related genes are termed DC-like monocytes (*4*).

To further pinpoint monocyte origins, a fate-mapping system was used to track and trace their development. The GMP fate-mapping mouse (*Ms4a3*^{Cre}:*Rosa*^{TdTomato}) surprisingly revealed that the majority of monocytes (~95%) originated from GMPs, whereas only a small fraction of *Cd209a*-expressing cells (~3 to 5%) remained unlabeled, indicating their MDP origin (*5*). Owing to their distinct DC signature, including labeling in *Zbtb46*$^{Gfp/Gfp}$ mice and antigen-presenting abilities, MDP-derived cells were classified as blood pro-DC3s, which give rise to tissue DC3s (*5*). These cells are equivalent to the human DC3 counterpart, which also shares several overlapping characteristics with both monocytes and cDCs but lacks the

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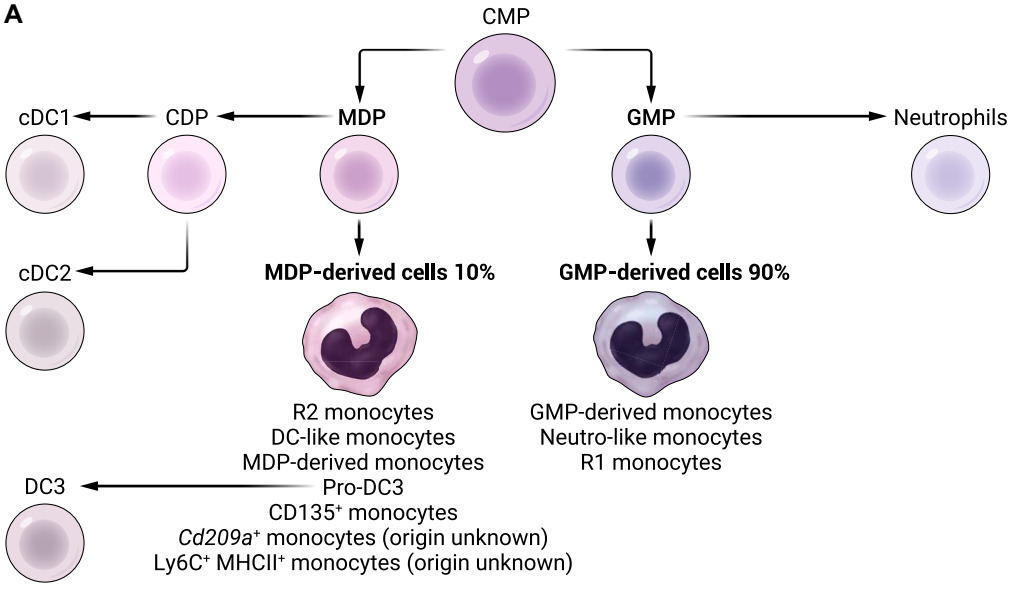
A



B

	Given name	Surface markers (protein)	Transcription	Other characteristics
Ly6C⁺ CD115⁺ cells: MDP-derived	R2 monocytes[7]	Ly6C⁺, CD135⁺, CD11b⁺, CD172a⁺, CD11c⁻, MHCII⁺	*Cd209a, Clec9a, Slamf7, FLT3L*	Not labelled in Zbtb46$^{Gfp/+}$ mice; Flt3L independent, CSF2, CCR2, and PU.1^{Hi} dependent
	DC-like monocytes[4]	Ly6C^{High}, CD11b⁺, CD11c⁺, MHCII⁺	*Cd209a, H2-Ab1, FLT3L*	Expansion in vitro with CSF2; increase after CpG injection
	MDP-derived or CD319⁺ monocytes[9]	Ly6C^{High}, CD135⁻, CD11b⁺, CD319⁺, CD177⁻	*Cd209a, Slamf7, Clec10a, Tmem176a*	Negative for ZBTB46 (by flow cytometry); increase after CpG injection
	Pro-DC3[5]	Ly6C⁺, CD135⁺, CD11b⁺, CD45RB⁺, CD11c⁻, MHCII⁻	*Cd209a, Cd74, Lyz2, Tmem176a*	Labelled in Zbtb46$^{Gfp/+}$ mice; *Klf4* and *Irf8* dependent; induce OTII T cell proliferation
	CD135⁺ monocytes[8]	Ly6C$^{Hi\text{-}to\text{-}Int}$, CD135⁺, CD11b⁺, CD172a⁺, CD11c⁺, MHCII⁺, CD301a⁺	*Cd209a, Cd74, Clec10a, Mrc1*	Flt3L dependent, CSF2 independent stimulate T cells in allogenic MLR assay
n.d.	*Cd209a*⁺ monocytes[3]	Ly6C⁺, CD11b⁺	*Cd209a, Cd74, Ccr2, Tmem176a, Slamf7*	
	Ly6C⁺ MHCII⁺ [2]	Ly6C⁺, MHCII⁺	*Cd209a, Cd74, H2-Ab1, Slamf7*	Immgen.org
GMP-derived	GMP-derived or CD177⁺ monocytes[9]	Ly6C^{Hi}, CD319⁻, partially CD177⁺	*Sell, Chil3, Cd177, Cebpb*	Increase after LPS injection
	Neutro-like monocytes[4]	Ly6C^{Hi}, MPO	*Elane, Prtn3, Ctsg, Serpinb1a*	Increase after LPS injection
	R1 monocytes[7]	Ly6C^{Hi}, CD172a⁺, CD135⁻	*Msr1, Ctsg, Mpo, Mmp8, Elane*	Generate iNOS⁺ cells during *Listeria* infection

Fig. 1. The dual origin of classical monocytes. (**A**) Cells that phenocopy classical monocytes can derive from MDPs (left) and GMPs (right). However, it is unclear whether all reported MDP-derived cell subsets represent distinct entities or whether they are essentially identical doppelgängers, corresponding to the same cell population. The same holds true for the three GMP-derived cell subsets, but they likely reflect the same population. (**B**) Table categorizing all Ly6C⁺ and CD115⁺ subsets reported so far. n.d., origin not determined; CMP, common myeloid progenitor; cDC, conventional dendritic cell.

monocyte markers CD88 and CD89 (*6*). These data challenged the notion that MDPs are precursors of monocytes and established a new paradigm in which classical monocytes actually originate from GMPs. On the basis of these results, the previously reported neutro-like monocytes (*4*) or "R1" cells (*7*) may correspond to classical monocytes, whereas DC-like monocytes (*4*), R2 cells (*7*), CD135$^+$ monocytes (*8*), and *Cd209*$^+$ cells (*3*) appear to have some features of pro-DC3s (Fig. 1B).

An additional piece of this ontological puzzle was recently added by findings obtained with a double reporter mouse system, namely, *Ms4a3*^{Cre}*:Rosa*^{TdTomato} GMP fate-mapper mice crossed with *Cx3cr1*^{Gfp} mononuclear phagocyte reporter mice. In this model, two Ly6C^{Hi} monocyte subsets were detected within the bone marrow and peripheral circulation: a double-labeled CD319$^-$ GMP-derived monocyte subset (~90% of the classical monocyte gate) and a smaller fraction of Ly6C$^+$ CD319$^+$ MDP-derived cells characterized by only GFP expression (~10%). These MDP-derived cells expressed certain DC3 genes (*Cd209a*, *Tmem176a*, and *Cd74*) but lacked the expression of the key DC markers FLT3, ZBTB46, and CD11c (Fig. 1B) (*9*). Consequently, it was proposed that CD319$^+$ MDP-derived cells do not belong to the DC lineage but rather represent a classical monocyte subset (*9*). These data are consistent with the observations that R2 cells were not labeled in heterozygous *Zbtb46*$^{Gfp/+}$ mice and developed independently of FLT3L despite expressing CD135 (*7*), which justifies their inclusion in the monocyte lineage.

The outcomes of these studies parallel Dostoevsky's doppelgänger motif: Do MDP-derived pro-DC3s and CD319$^+$ cells constitute the same population or two distinct entities that share a partially overlapping transcriptional program (Fig. 1A)? This is not merely a matter of semantics but could have significant implications for the physiological and pathological functions of these cells. If MDP-derived cells are equivalent to pro-DC3s, then they should have the ability to present antigens and migrate to lymph nodes. Indeed, DC3s are capable of presenting antigens and play an essential role in T_H17 polarization, whereas monocyte-derived cells perform poorly in these assays (*5*). Therefore, it remains to be determined whether CD319$^+$ MDP-derived cells are capable of and involved in antigen presentation. Conversely, if MDP-derived CD319$^+$ cells belong to the monocyte family, then they should have the potential to infiltrate tissues and develop into CSF1R-dependent macrophages. In fact, both GMP- and MDP-derived populations have been shown to infiltrate the lungs and gut and differentiate into tissue-resident cells after adoptive transfer experiments (*9*). Curiously, only MDP-derived cells demonstrate the ability to colonize the dura mater after experimental elimination of endogenous macrophages from this particular niche (*9*). Another recent study examined whether ontologically distinct GMP- or MDP-derived subsets have different capabilities to repopulate the skin epidermal Langerhans cell (LC) pool after their destruction in a mouse model of graft-versus-host disease (GvHD). Given that LCs display functions of DCs, such as migration to draining lymph nodes during pathological processes, it can be inferred that the DC-like characteristics of LCs are possibly a legacy of their origin. Surprisingly though, both GMP- and MDP-derived cells accumulated in the skin and subsequently gave rise to LCs (*10*).

Although tissue residency is a defining feature of macrophages, DCs also function as homeostatic tissue–resident immune cells. Initial findings indicate that DC3s can be found in various tissues under steady-state conditions (*11*), challenging the idea that tissue residency is unique to macrophages. However, unlike long-lived self-renewing tissue macrophages, cDCs are short lived and require continuous replenishment from the bone marrow. Examining the retention time of cells derived from GMPs or MDPs within tissues could offer valuable insight into their cellular identity. However, current studies have only examined GMP- or MDP-derived cells in tissues up to 12 days after transfer (*9*), or, in the context of LC replacement during GvHD, it remains to be determined whether GMP- or MDP-derived LCs dominate the niche over time because of differences in longevity and proliferation (*10*). Additional evidence is required to determine whether tissue-infiltrating GMP- or MDP-derived cells depend either on FLT3 (and its ligand FLT3L) or CSF1R (and its ligands CSF1 or IL-34) for their development and express ZBTB46 after differentiation, which could act as a crucial criterion for lineage determination.

Another characteristic of classical monocytes is their capacity to develop into nonclassical monocytes. It is therefore reasonable to ask whether both GMP-derived monocytes and MDP-derived cells have the ability to convert into nonclassical monocytes. Nonclassical monocytes may be viewed as terminally differentiated macrophages residing in the blood (*12*). Recent findings indicate that the survival of nonclassical monocytes relies on their interaction with the vascular endothelium, which is facilitated by the CX_3CL1-CX_3CR1 axis and LFA-1. This interaction permits nonclassical monocytes to bind to CSF1 tethered to the endothelium, which is a crucial factor for their survival (*13*). Concerning their origin, transfer and fate-mapping experiments have shown that nonclassical monocytes arise from classical monocytes in rodents and humans (*1*). scRNA-seq profiling has revealed that nonclassical monocytes are connected to GMP-derived classical monocytes through an intermediate stage, but they do not appear to be related to *Cd209a*-expressing cells, which are likely to be derived from MDPs (*3*). However, when Ly6C^{Hi} GMP- or MDP-derived cells are transferred into the bloodstream of recipient mice, both cell types gradually lose their Ly6C expression over time and phenotypically resemble nonclassical monocytes. Upon the investigation of a few surface markers, only programmed death-ligand 1 (PD-L1) was found to be differentially expressed between GMP- and MDP-derived Ly6C^{Low} cells (*9*). Alternatively, if the injected MDP-derived cells are pro-DC3s, then it is possible that they lose Ly6C expression during their development into Ly6C$^-$ DC3s after transfer (*5*). The transcriptomic signature of these transferred cells and the potential heterogeneity within the nonclassical monocyte pool remain uncertain.

THE ROLE OF MONOCYTE HETEROGENEITY DURING PATHOLOGY

The existence of various classical monocyte-like populations suggests that each subset may fulfill a distinct function that collectively contributes to a coordinated immune response. Supporting this idea, studies have demonstrated that bacterial LPS injection results in an increase in GMP-derived monocytes, whereas CpG injection, mimicking viral infection, leads to an increase in MDP-derived cells (*4*, *9*). iNOS$^+$ macrophages are a characteristic feature of *Listeria monocytogenes* infection and originate from circulating classical monocytes (*14*). Given the heterogeneity among classical monocytes,

it is plausible that only a specific subset can acquire certain specialized phenotypes during differentiation. Indeed, in vitro and in vivo studies have confirmed that R1 or GMP-derived classical monocytes are uniquely able to produce iNOS$^+$ macrophages after exposure to *L. monocytogenes* (*7*).

Significant progress has been made in the context of solid tumors and inflammation, in which a conserved molecular "state" of cDCs has recently been identified. These cells are termed "mature DCs enriched in immunoregulatory molecules" or mregDCs (*15*) and are characterized by the expression of *LAMP3*, *PDCD1LG2*, and *CCR7*, which are associated with regulatory, immunogenic, and migratory gene programs. It appears that both cDC1 and cDC2 subsets can acquire an mregDC state upon interacting with or internalizing cell-associated antigens (*15*). Therefore, it is plausible that pro-DC3s may also differentiate into mregDCs when exposed to the tumor environment. Additionally, R2 or MDP-derived cells can up-regulate *PDCD1LG2* in a PU.1- and CSF2-dependent manner (*7*). Nonetheless, the specific contribution of this subset to cancer development requires further investigation.

CONCLUSION

The identification of several monocyte doppelgänger populations has significant implications for laboratory research. Relying solely on traditional methods that use a limited set of markers to identify classical monocytes does not do justice to the underlying heterogeneity and may overlook doppelgänger subsets masked as classical monocytes. For instance, relying on such methods could unintentionally include pro-DC3s, which could distort antigen-dependent T cell stimulation experiments. Moreover, classical monocyte-derived cells have been associated with a variety of diseases, including cardiovascular conditions, autoimmunity, cancer, and infections. It is crucial to determine whether the reported functions of classical monocytes in these pathological conditions can be attributed to classical monocytes or whether they are influenced by the presence of a specific monocyte subset and doppelgänger populations. This will require a reassessment of the role of each monocyte population in distinct disease contexts.

At this crossroads of monocyte research, it is essential to provide a clear and comprehensive definition of these cells that extends beyond their cytokine dependency, surface marker expression, and origin. This definition must also encompass functional aspects such as lymph node homing and antigen presentation. Thus, as Dostoevsky's Golyadkin remarks to his physician Rutenspitz, this definition may not emerge "…till a more convenient moment, when everything will be discovered and the mask falls off certain faces, and something comes to light."

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