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PERSPECTIVES

OPINION

Dendritic cells, monocytes and macrophages: a unified nomenclature based on ontogeny

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Abstract | The mononuclear phagocyte system (MPS) has historically been categorized into monocytes, dendritic cells and macrophages on the basis of functional and phenotypical characteristics. However, considering that these characteristics are often overlapping, the distinction between and classification of these cell types has been challenging. In this Opinion article, we propose a unified nomenclature for the MPS. We suggest that these cells can be classified primarily by their ontogeny and secondarily by their location, function and phenotype. We believe that this system permits a more robust classification during both steady-state and inflammatory conditions, with the benefit of spanning different tissues and across species.

Dendritic cells (DCs), monocytes and macrophages are members of the mononuclear phagocyte system (MPS) that exhibit multiple functions during immune responses. Historically, these cells have been grouped together because although monocytes have their unique functions as mononuclear phagocytic cells, they were also considered as the definitive precursors of macrophages and DCs[1–3] (BOX 1). Macrophages are distinguished as larger vacuolar cells that excel in the clearance of apoptotic cells, cellular debris and pathogens[4,5], and have been phenotypically defined in mice as F4/80^{hi} cells[6]. By contrast, DCs are usually defined as cells with a stellate morphology that can efficiently present antigens on MHC molecules and activate naive T cells[7,8]. In mice, DCs are defined as CD11c^{hi}MHC class II^{+} cells[9–11].

Since the original description of the MPS, the advent of polychromatic flow cytometry has enabled the assessment of different surface markers and allowed an unparalleled exploration of cellular phenotype and heterogeneity. This has facilitated the characterization of multiple distinct DC, monocyte and macrophage subsets in mice[12–14]. However, it has also revealed that many of the proposed unique markers and functions are, in fact, shared between cell types. Further complicating matters, markers of a particular cell subset are not always consistent between mice and humans. This has led to much confusion and debate regarding which subsets represent distinct cell types and which are simply modified versions of the same cell type[15].

The complexity of the current mononuclear phagocyte nomenclature can be illustrated by examining the situation in the intestine. DCs have been divided into many different subsets on the basis of the expression of some of the following surface markers: CD103 (also known as integrin αE), CD11b (also known as integrin αM), CX_3C-chemokine receptor 1 (CX_3CR1), F4/80, CD8α, CD24, CD172a (also known as SIRPα and SHPS1), XC-chemokine receptor 1 (XCR1), CLEC9A (also known as DNGR1), E-cadherin (also known as cadherin 1) and CD64 (also known as FcγRI). Although some researchers define monocyte-derived cells in the intestine as DCs or macrophages on the basis of their respective expression or lack of expression of CD11c[16,17], others consider many of these CD11c^{+} 'DCs' to, in fact, be 'macrophages' (REF. 18). Morphological analysis is equally ambiguous, as intestinal monocyte-derived cells possess transepithelial dendrites[19,20], leading some to consider these as DCs. Inflammation further complicates the picture, as mononuclear phagocytes in the inflamed intestine undergo phenotypical changes, and monocyte-derived cells that are not present in the steady-state intestine infiltrate during inflammation — for example, tumour necrosis factor (TNF)- and inducible nitric oxide synthase (iNOS)-producing DCs (TIP-DCs)[21–23].

Consequently, interpreting the published literature is a minefield, as the same cell type is often given a different name on the basis of a prescribed functional or phenotypical characteristic. Although one can argue that naming is arbitrary and unimportant — as it has no bearing on the function of a cell — it becomes a concern when there is poor consistency between laboratories that leads to assumptions, bias, miscommunication and confusion. It is important for us to demarcate fundamentally novel subsets in the immune system, as opposed to simply identifying yet another marker for an existing subset. We believe that the issue has now moved beyond an etymological debate or trivial semantics because the name that is given to these cells often implies a functional specialization.

In this Opinion article, we propose a unifying nomenclature for cells of the MPS, in which the cellular origin forms the principal basis for their classification. Although primarily based on data from the mouse immune system, we suggest that this nomenclature could also be used in humans and other species on the basis of transcriptional, phenotypical and functional interspecies homology.

A new nomenclature for the MPS

In the sections below, we suggest and describe a new nomenclature for the MPS that could be adopted by researchers in the field in order to overcome the issues highlighted above. In devising this nomenclature, we have used historical terms where possible but have primarily based the terminology on

Box 1 | **A historical perspective**

The preliminary studies on mononuclear phagocytes occurred at the same time as the publication of the histological accounts of von Recklinghausen (1863)[125]. Nonetheless, it was Ilya Metchnikoff (1892) — the father of cellular immunity — who established the phagocyte system[4,5,126]. Metchnikoff was the first to fully comprehend the capabilities of phagocytes, by carrying out a series of classical studies spanning from the echinoderm amoebocyte to the vertebrate. The phagocyte system comprised cells that he termed macrophages (from the Greek for 'large eaters') and microphages ('small eaters'; now known as polymorphonuclear leukocytes). Remarkably, Metchnikoff appreciated that phagocytosis is more than the ability of a cell to engulf foreign microorganisms and that it is also an active defence mechanism — this gave rise to the concept of innate immunity.

By the turn of the twentieth century, the phagocyte system had undergone a number of amendments and the term macrophage had become synonymous with erythrophagocyte, pyrrhol cell, adventitia cell, rhagiocrine cell, polyblast, clasmatocyte and histiocyte. The many names that have been assigned to these cells reflected the divergence of opinion at the time as to the relationships between these cells. Ribbert (1904) restored order to the macrophage system when he discovered that diluted lithium carmine that is injected intravenously is specifically taken up by a group of cells, which became 'vitally stained' (REF. 127). Aschoff[128] coined the name 'reticulo endothelial system' (RES) to describe this group of cells. Shortly after the RES was introduced, a number of laboratories were in pursuit of the origin of these macrophages. Several *in vitro* studies that were published in close succession described the transformation of circulating monocytes into macrophages[129–131]. Carrel and Ebbing[129] observed that, over time, blood cultures became primarily composed of monocyte-derived macrophages that had phagocytosed the relics of the other blood cells. However, it was the set of elegant experiments carried out by Ebert and Florey[132], using the rabbit ear chamber, that first showed mammalian blood monocytes actively migrating towards sites of injury and differentiating into macrophages *in vivo*. Subsequently, Volkman and Gowans[133] demonstrated, with the aid of thymidine autoradiography, that these infiltrating macrophages originate from the bone marrow. These new technologies (thymidine autoradiography, immunohistochemistry, parabiosis and electron microscopy) highlighted that the cells of the RES differ in morphology, function and origin[134].

By the late 1960s, a group of leading scientists — including Ralph van Furth, James G. Hirsch and Zanvil A. Cohn — formulated the 'mononuclear phagocyte system' (MPS)[1]. The MPS constituted monocytes and macrophages with the premise that all macrophages are derived from blood monocytes. Nevertheless, scant evidence existed to suggest that monocytes differentiate into tissue-resident macrophage populations. On the contrary, it was acknowledged that macrophages exist in lower multicellular organisms, such as *Porifera* (sponges), in the absence of circulating monocytes[135,136]. Furthermore, as early as 1907, Maximow[137] concluded from embryonic studies in amphibians, rodents and larger mammals that macrophages and leukocytes arise from separate lineages.

While the MPS was being devised in the 1960s, scientists were in pursuit of the 'third cell' (REF. 138) required for adaptive immune responses. In the 1970s, Steinman identified and characterized the dendritic cell (DC)[7,8]. This seminal discovery redefined our understanding of the immune response. Nevertheless, the identification of the DC has caused much debate among scientists about whether the DC is a constituent of the MPS or not. It should be noted that shortly after Steinman's discovery, van Furth incorporated DCs into the MPS[139]. Since then, monocytes, macrophages and DCs have been grouped together, and they are distinguished on the basis of their morphology, function and origin. Several attempts to formulate an inclusive system encompassing monocytes, macrophages and DCs have included the 'custocyte system' and the 'mononuclear–phagocyte and immunoregulatory effector (M-PIRE) system' (REFS 140,141).

Yet again, we have reached a crossroads in MPS nomenclature. Lineage-tracing studies have demonstrated that, under steady-state conditions, most macrophages in adults are maintained independently of blood monocytes and rely almost exclusively on self-renewal[24–30,32,73]. They have also shown that classical DCs arise from adult haematopoietic stem cell (HSC)-derived common DC precursors (CDPs) that are distinct from classical monocytes[46,47]. These findings highlight that the MPS is not a closed monocyte–macrophage system as originally proposed but instead that the MPS encompasses three broad families of cells — namely, CDP-derived DCs, embryonic-derived macrophages and monocyte-derived cells.

a two-level system. We propose that mononuclear phagocytes should first be defined on the basis of their ontogeny (level one) and that these cells can subsequently be classified on the basis of their function, location and/or phenotype (level two). We think that this approach will yield a more robust nomenclature for mononuclear phagocytes, generating mutually exclusive level one selection criteria that are conserved across tissues and species. Of course, further discussion will be needed among the international research community before these — or an improved version of these — recommendations are accepted as an official nomenclature, and we propose to discuss this during round table sessions organized at upcoming international DC and macrophage meetings. Indeed, the aim of this article is not to be overly prescriptive but instead it is an attempt to propose a refined and less ambiguous MPS nomenclature in order to facilitate communication between different research groups.

Level one nomenclature. Terminally differentiated cells of the MPS were initially thought to derive exclusively from blood monocytes. However, the ontogeny of the MPS has undergone a conceptual revolution with three key recent findings. First, most adult macrophages are predominantly maintained through self-renewal, independently of adult haematopoiesis, and derive from precursors that arise during embryonic development[24–30,73,142]. Second, monocytes arise from precursor cells that are committed to the monocyte lineage — so-called common monocyte progenitors (cMoPs)[31]. Monocytes can traffic to tissues and maintain their phenotype in the steady state[32,33] but they can also give rise to cells with a vast array of functions depending on the microenvironment in which they reside[16,33,34]. Third, conventional or classical DCs (cDCs) and plasmacytoid DCs (pDCs) — but not monocytes and macrophages — arise from a common DC precursor (CDP)[35,36]. We therefore propose the initial division of mononuclear phagocytes into three main categories — namely, macrophages, monocytes (and monocyte-derived cells) and DCs (FIG. 1).

Level two nomenclature. As MPS research mostly focuses on function, and not cellular origin, we supplement our level one nomenclature with a level two nomenclature by allowing the addition of a marker or functional property as an optional and flexible feature of the naming scheme. The overarching principal of this format is to allow scientists to freely describe the features of their cell of interest but also encourage them to place it in the context of its cellular origin. Although allowing flexibility in level two nomenclature could add confusion, we believe it allows the evolution of terminology, concomitant with evolving knowledge of function. The stringency of level one should provide sufficient structure in the nomenclature and provide the best compromise at this juncture. We propose that the level one nomenclature — which has a restricted set of options — trumps the level two nomenclature when classifying cells, as is illustrated by the examples shown in FIG. 2.

Classifying mouse dendritic cells

We propose that DCs should be classified as a separate lineage of mononuclear phagocytes on the basis of the fact that they arise from adult haematopoietic stem cell (HSC)-derived precursors that are distinct from the precursors of monocytes and macrophages (FIG. 1). We further propose to subdivide DCs into only three main subtypes — two main lineages of cDCs (which we propose should be called 'classical type 1 DCs (cDC1s)' for $CD8\alpha^+$ and $CD103^+$ DCs, and 'cDC2s' for $CD11b^+$ and $CD172a^+$ DCs, on the basis of their distinct developmental pathways) and pDCs, which retain their original name.

When devising a nomenclature for the different DC subtypes, we were aware of similar previous attempts to achieve this using numbering systems that have not subsequently been adopted by the field[37,38]. However, we still believe that a numbering system helps to simplify the nomenclature across tissues and species, and we suggest that the inclusion of a 'c' for 'conventional' or 'classical' that has been in use for many years[39] discriminates our proposed nomenclature sufficiently from prior attempts. Importantly, we do not mean to imply that cDC1s and cDC2s always regulate T helper 1 (T_H1)-type and T_H2-type immune responses, respectively, although a functional parallel has been observed[40–45]. In our proposed nomenclature, pDCs (also known as interferon (IFN)-producing cells or IPCs) would also keep their name. Although they are morphologically closer to plasma cells, their development correlates with that of cDCs[35,36,46,48]. Moreover, they can assume a dendritic appearance upon activation and can influence T cell fate, so we feel that this justifies their categorization as DCs.

At which point of their development DCs first branch from other cell lineages is still a matter of debate. There is evidence to suggest that this may occur at a relatively early stage of haematopoiesis[46] and it is clear that DCs can develop from CDPs in the bone marrow[35,36]. CDPs give rise to distinct DC subtypes[35,36] and cellular markers have been identified that help to delineate distinct CDP populations that are biased towards the generation of either cDCs or pDCs[35,36,47,48]. The intermediate stage between CDPs and cDCs is the precursor for cDCs (the pre-cDC). These pre-cDCs develop from CDPs in the bone marrow and then migrate to peripheral organs where they develop locally into cDCs[49–51,58]. On the other hand, pDCs terminally differentiate

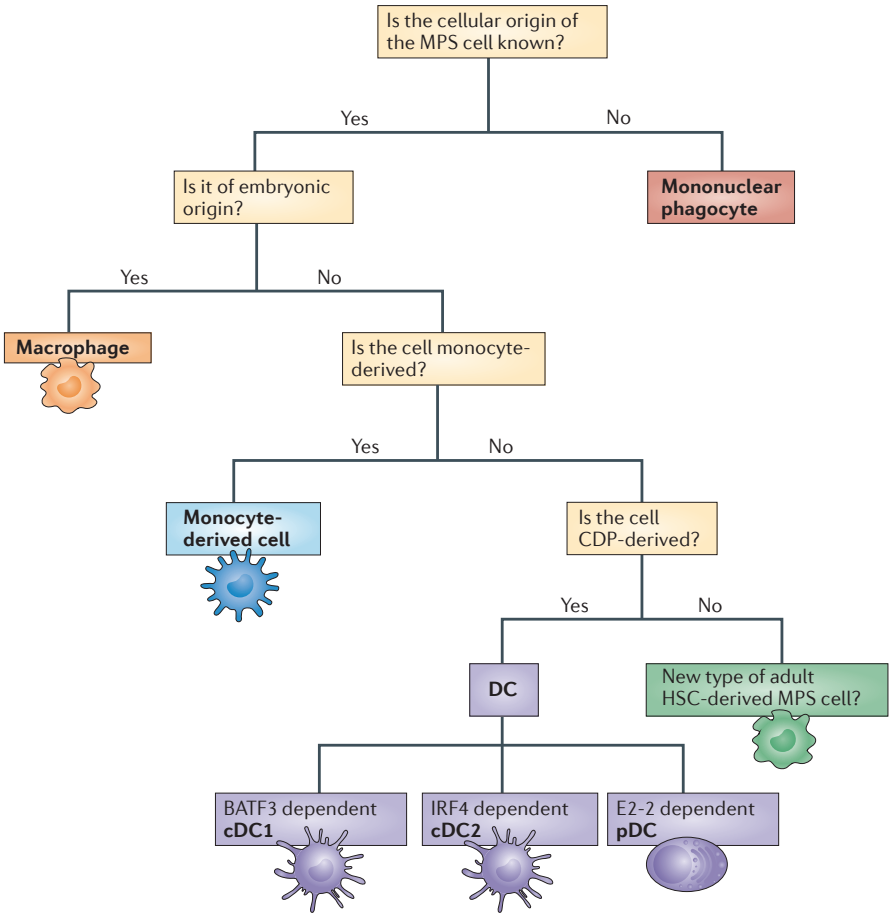

Figure 1 | **A decision tree to facilitate nomenclature decisions for mononuclear phagocytes.** We propose that mononuclear phagocytes would primarily be categorized according to their ontogeny (level one nomenclature). Although the ontogenetic nomenclature aims to prevent the miscategorization of cells, we fully acknowledge that studies pertaining to cellular origin are not always feasible. Furthermore, adopting an ontogeny-based nomenclature for mononuclear phagocytes in other species, such as humans, remains challenging. We suggest that when cell transfers are unfeasible and fate-mapping or genetic ablation models are not available, a parallel nomenclature should be used. This level two nomenclature will identify mononuclear phagocyte subsets on the basis of their expression of conserved phenotypical markers or transcripts (not shown). See Supplementary Information S1 (table) and S2 (table) for details of the markers that can be used to aid classification decisions in mice and humans. Cells of embryonic origin would be referred to as 'macrophages' (orange box). Note that some macrophages have historical names such as 'Langerhans cells', 'Kupffer cells' or 'microglia' and we propose to keep these terms. Others would be categorized as, for example, 'peritoneal macrophages' or 'alveolar macrophages'. Mononuclear phagocyte system (MPS) cells of uncertain origin would be referred to as 'mononuclear phagocytes' (red box) and be further categorized on the basis of their functional or phenotypical properties and their tissue localization (level two classification). This aims to prevent the miscategorization of MPS cells and should facilitate scientific communication. MPS cells derived from monocytes would be referred to as 'monocyte-derived cells' (blue box). Note that these cells are very plastic and can acquire functional properties of both dendritic cells (DCs) and macrophages in some settings. Monocyte-derived cells would be further categorized according to functional specialization, phenotypical properties and transcriptional networks under level two nomenclature. Monocytes, DCs and macrophages were historically grouped in the MPS (see BOX 1), and for continuity, we propose to maintain this classification. Hypothetically, if a new immune cell type is identified with a distinct cellular origin from monocytes, DCs and macrophages (green box), it is difficult to determine whether they should be incorporated into the MPS or not. This is because the current cells within the MPS are not developmentally linked and have no obvious functional property in common that would distinguish them from other immune cells. We suggest that transcriptional profiling could be used to determine whether any newly identified cell has important homology with monocytes, DCs or macrophages. This would open the possibility of incorporating a new cell type into the MPS. BATF3, basic leucine zipper transcriptional factor ATF-like 3; cDC1, classical type 1 DC; cDC2, classical type 2 DC; CDP, common DC precursor; HSC, haematopoietic stem cell; IRF4, interferon-regulatory factor 4.

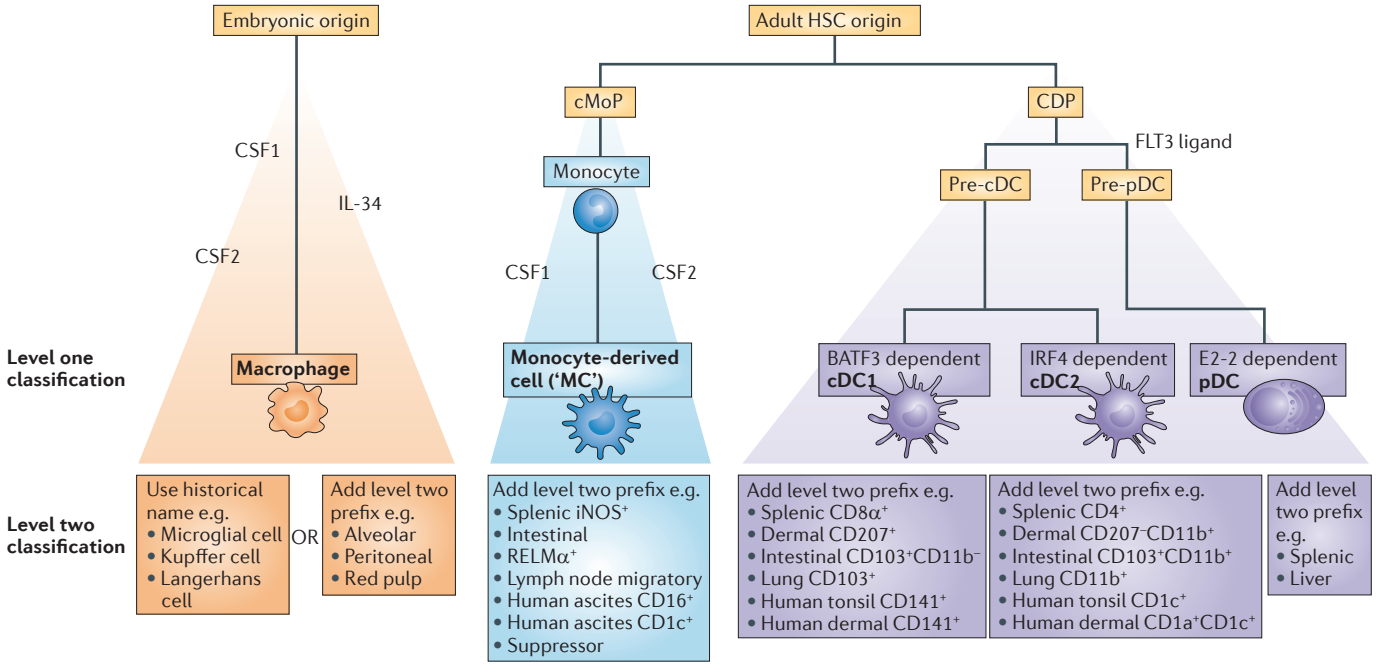

Figure 2 | **Two levels of nomenclature for classifying mononuclear phagocytes.** We suggest that mononuclear phagocytes should first be defined on the basis of their ontogeny (level one nomenclature; yellow boxes), followed by their function, location and/or morphology (level two nomenclature; blue boxes). This yields three main groups of cells — namely, common dendritic cell (DC) precursor (CDP)-derived DCs, embryonic-derived macrophages and monocyte-derived cells. We suggest that DCs should be further subdivided into 'classical type 1 DCs (cDC1s)', 'cDC2s' and plasmacytoid DCs (pDCs) because their development depends on distinct sets of transcription factors and because they arise from discrete committed precursors. In the lower part of the figure, we have added some examples to illustrate how our approach can yield a unifying nomenclature without losing flexibility. Level one nomenclature also includes unambiguous and widely accepted historical names (green box). Level two nomenclature can include surface markers that are used to identify the cells, the functional specialization studied or information on cell localization. Examples of level two nomenclature are provided, however, in many cases, level one should be sufficient to adequately define a population, except when a novel function and/or relevant marker is required to discern a particular cell subset. We suggest the use of 'MC' as an abbreviation for monocyte-derived cells. However, this is not an officially accepted abbreviation and is incorporated here merely as a suggestion. BATF3, basic leucine zipper transcriptional factor ATF-like 3; cMoP, common monocyte progenitor; CSF1, colony-stimulating factor 1 (also known as M-CSF); CSF2, colony-stimulating factor 2 (also known as GM-CSF); FLT3, FMS-like tyrosine kinase 3; HSC, haematopoietic stem cell; IL-34, interleukin-34; iNOS, inducible nitric oxide synthase; IRF4, interferon-regulatory factor 4; RELMα, resistin-like molecule-α.

from CDPs in the bone marrow via a pre-pDC intermediate stage[36,48,52,53]. Note that it has been proposed that some pDCs may arise from a lymphoid precursor[54,55].

Although the development of all DC subsets is mostly dependent on the cytokine FMS-like tyrosine kinase 3 ligand (FLT3L)[56–58], differentiation into DC subtypes is specifically controlled by distinct sets of transcription factors. Mice lacking IFN-regulatory factor 8 (IRF8)[59], DNA-binding protein inhibitor ID2 (REFS 58,60), basic leucine zipper transcriptional factor ATF-like 3 (BATF3)[61] or nuclear factor interleukin (IL)-3-regulated protein (NFIL3)[62] exhibit a severe defect in the development of cDC1s, whereas cDC2 development is strongly controlled by RELB[63], PU.1 (REF. 64), recombining binding protein suppressor of hairless (RBPJ)[65–67] and IRF4 (REFS 42,68,69). Notably, under certain inflammatory settings a few splenic cDC1s are still able to develop in the absence of BATF3, ID2 and NFIL3 (REF. 70). The development of pDCs is regulated by the transcription factor E2-2 (also known as TCF4)[71,72], which counteracts the actions of ID2 that are required for cDC1 development. Several targets of E2-2 — such as SPIB, IRF7 and IRF8 — contribute to pDC lineage specification, and E2-2 is thus regarded as the 'master regulator' of pDCs[71,72].

Mouse macrophages

Recent studies have shown that the majority of macrophages are derived from embryonic progenitors[24–30,73,74], which include yolk sac-derived macrophages and fetal monocytes (as recently review in REF. 13). When the circulation is established, these cells spread via the blood into peripheral tissues of the fetus, giving rise to tissue-resident macrophages that self-maintain throughout life. Their development is highly dependent on macrophage colony-stimulating factor 1 receptor (CSF1R; also known as M-CSFR), which is the receptor for the cytokines colony-stimulating factor 1 (CSF1; also known as M-CSF) and IL-34. These cytokines are crucial for the differentiation and survival of most macrophages[75,76,143].

On the basis of their shared embryonic origins, we suggest that microglia, Kupffer cells, alveolar macrophages and splenic red pulp macrophages should be defined as part of the macrophage family but we propose to keep their historical names (FIG. 2). Although Langerhans cells share many functional properties with cDCs, we suggest that these cells should also be classified as macrophages on the basis of their embryonic origin. Importantly, despite grouping these cells as one family, gene expression analysis of macrophages from various tissues has demonstrated the astonishing diversity of these cells[77], suggesting that each macrophage population is specifically adapted to its tissue of residence[78,79]. However, we suggest that any newly identified mononuclear phagocyte of embryonic origin should be classified as a macrophage.

Mouse monocyte-derived cells

Mouse monocytes consist of two subtypes — namely, LY6C^{hi} classical monocytes and LY6C^{low} non-classical monocytes[80]. LY6C^{hi} classical monocytes derive from the recently identified cMoP[31]. Undifferentiated LY6C^{hi} classical monocytes are not only found in the blood but also in several steady-state tissues, including the spleen, lymph nodes, skin and lungs[32,33,81]. LY6C^{low} non-classical monocytes remain mostly within the blood vessels where they patrol the vascular wall[82]. Whether all LY6C^{low} blood monocytes differentiate from LY6C^{hi} monocytes[83,84,25] is still a matter of debate. Until this is firmly established, we retain the term LY6C^{low} non-classical monocytes. By contrast, LY6C^{hi} classical monocytes are the definitive precursors of many mononuclear phagocytes and in certain adult tissues — including the gut, heart and dermis — these cells rely on continuous monocytic input for their maintenance in the steady state[16,33,85]. Strikingly, inflammation is often associated with such a substantial influx of monocytes[80,86,87,144] that these cells can outnumber cDCs and macrophages. LY6C^{hi} monocyte-derived cells have been classified as monocyte-derived DCs, monocyte-derived macrophages or myeloid-derived suppressor cells (MDSCs) on the basis of a set of restricted but non-exclusive functional properties that can be difficult to robustly assess *in vivo*.

Like cDCs, monocyte-derived cells can express CD11c and MHC class II, and they can present antigen to induce naive T cell activation[44,88,89]. However, similarly to macrophages, they can express F4/80, the tyrosine protein kinase MER (MERTK) and CD64, and they are efficient at phagocytosis and often poor at migration[23,33,44,90]. Monocyte-derived cells are often highly heterogeneous, even within a single organ or inflamed tissue. Therefore, it remains unclear whether monocyte-derived DCs and monocyte-derived macrophages constitute two ontogenically distinct lineages that are controlled by distinct sets of molecular regulators (as demonstrated for cDC1s and cDC2s) or if they are, instead, highly plastic cells that are able to acquire a multitude of functional modules in response to the cues they receive from their microenvironment.

Currently, there is a lack of suitable methods to accurately discriminate between different populations of monocyte-derived cells in adults. Therefore, we propose to regroup these cells under a single level one term — namely, 'monocyte-derived cells'. Importantly, we do not deny that monocyte-derived cells can acquire functional properties that are very similar to cDCs (including migrating to the lymph nodes and activating naive T cells) or to macrophages (for example, they can participate in pathogen killing, phagocytosis or tissue repair responses) depending on the context in which they develop.

We therefore suggest that the level two nomenclature could be used to underline the functional heterogeneity of monocyte-derived cells (FIG. 2). As 'monocyte-derived cell' is quite long, we propose that this term could be abbreviated to 'MC'. For instance, we suggest that TIP-DCs could be called 'iNOS$^+$ MCs' to underline both their monocytic origin[21,91] (level one nomenclature) and their iNOS-mediated killing capabilities (level two nomenclature). We would term the monocyte-derived cells that are found in the steady-state intestine 'intestinal MCs'. When monocyte-derived cells migrate to the lymph nodes, we would propose to call these cells 'lymph node migratory MCs'. We would equally favour the use of 'arginase$^+$ MCs' or 'RELMα$^+$ MCs' (which express resistin-like molecule-α), for example. If monocyte-derived cells show suppressive activity, they could be called 'suppressive MCs' instead of MDSCs. Note that MC is not an officially accepted abbreviation and is incorporated here merely as a suggestion.

Translation to the human immune system

Although the MPS is well established in humans, determining cell ontogeny remains a challenge. As such, our proposed nomenclature scheme is predominantly based on evidence from mice. Nonetheless, we believe that a parallel nomenclature can be used in humans on the basis of transcriptomic and phenotypic profiling studies[42,92–94,104] that have shown an important level of homology between mouse and human mononuclear phagocyte populations. This has also been done in other species such as sheep, chicken, macaques and pigs[95–100]. Therefore, on the basis of this homology, we suggest that it could be feasible to apply the level one and level two nomenclature to the human immune system. To further facilitate the translation from mouse to humans, we have compiled tables that indicate the surface markers that are most commonly used to identify distinct mononuclear phagocyte populations in both species (see Supplementary Information S1 (table) and S2 (table)).

Dendritic cell populations in humans. Historically, human DCs found in lymphoid and non-lymphoid tissues were classified into two main groups — namely, pDCs and 'classical' or 'myeloid' DCs. Classical or myeloid DCs have been further subdivided into two subsets on the basis of their expression of CD141 (also known as BDCA3 and thrombomodulin) and CD1c (also known as BDCA1)[37,42,101–105]. It has been shown that the gene-expression profiles and functions of human CD141$^+$ DCs and CD1c$^+$ DCs resemble those of mouse cDC1s and cDC2s, respectively[92,104,106–110]. Accordingly, we propose that human CD141$^+$ DCs could be referred to as cDC1s and human CD1c$^+$ DCs referred to as cDC2s in a unifying nomenclature scheme. Further support for the equivalence of the mouse and human DC systems is that the injection of FLT3L into human volunteers dramatically increased the number of blood pDCs, CD141$^+$ cDCs (cDC1s) and CD1c$^+$ (cDC2s)[111]. In addition, E2-2, BATF3 and IRF4 have been proposed to act as master transcription factors for human pDCs[72], CD141$^+$ cDCs (cDC1s)[112] and CD1c$^+$ DCs (cDC2s)[42,113], respectively.

Macrophages in humans. Human macrophages are found throughout the body. During HSC transplantation, dermal macrophages in the recipient show prolonged survival and slower replacement compared with dermal DCs, which is consistent with the idea that macrophages are also self-maintaining in humans[114]. Furthermore, patients harbouring a mutation in *GATA2* (which encodes GATA-binding protein 2) lack blood monocytes and all cDC subsets, yet they have normal numbers of Langerhans cells and macrophages in the skin and lungs, respectively, suggesting that the development of these populations is independent of monocytes and DCs[115]. In a case of limb transplantation, Langerhans cells in the transplanted limb were still of donor origin 10 years after transplantation[116], which also supports the idea that human Langerhans cells are self-renewing, as is the case in mice. Therefore, there is accumulating evidence that human macrophages show similar properties to mouse macrophages.

Human monocyte-derived cells. Human blood monocytes are defined as CD14$^+$CD16$^-$ 'classical', CD14$^+$CD16$^+$ 'intermediate' and CD14^{low}CD16$^+$ 'non-classical' monocytes[37]. Transcriptomic analyses have demonstrated that CD14^{low}CD16$^+$ human monocytes are the counterparts of

LY6C^{low} non-classical mouse monocytes and that CD14$^+$CD16$^-$ human monocytes the counterparts of LY6C$^+$ classical mouse monocytes[117,118]. However, it is not clear exactly which human cells are monocyte derived. Transcriptomic analyses suggest that dermal CD14$^+$ DCs and intestinal CD103$^-$CD172a$^+$ DCs are related to monocytes[104,113], and that they potentially represent populations of monocyte-derived cells. In inflamed tissues, the 'inflammatory DCs' expressing CD1c, CD1a and CD14 are also likely to be monocyte-derived cells[119,120].

Devising a human MPS nomenclature. As exploring cell ontogeny in humans is challenging, we propose that human mononuclear phagocyte subtypes could be classified on the basis of conserved phenotypic markers and transcriptomic analyses. Although some specialized functions of DC subsets (for example, the secretion of type I (IFN) by pDCs[121] or type III IFNs by cDC1s[122]) are conserved between species, other functional specializations do not seem to be conserved (for example, cross-presentation and IL12p70 secretion by cDC1s[123,124]). We believe that this illustrates the strength of a nomenclature strategy that is based primarily on ontogeny, rather than on function, such that it can be applied across species.

Conclusion

In this Opinion article, we suggest that a new unified nomenclature for cells of the MPS will benefit the scientific community. We believe that distinguishing cells on the basis of their ontogeny will ensure a more robust classification of mononuclear phagocytes during steady-state and inflammatory conditions in different tissues across species. This should, in turn, allow for further studies of their functions in different contexts while avoiding some of the current confusion. In FIG. 2, we illustrate how our approach can yield a unifying nomenclature without losing flexibility. With ontogeny at the foundation of identifying mononuclear phagocytes, we also hope to avoid the ever-expanding number of mononuclear phagocyte subsets. Only when a cell type fulfils certain key criteria (FIG. 1) would a new level one name be ascribed.

We believe that applying a unified nomenclature across tissues and species will improve our understanding of mononuclear phagocyte function and benefit scientific communication both within and outside the field. However, we fully appreciate that this is a work in progress that will require further refinement as we gain a better understanding of the haematopoietic system. A final nomenclature system should be discussed with a wider panel of experts before acceptance by official nomenclature committees[37]. Nevertheless, we hope that the core principles that are described in this Opinion article will be helpful for finding a practical solution.

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Competing interests statement

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