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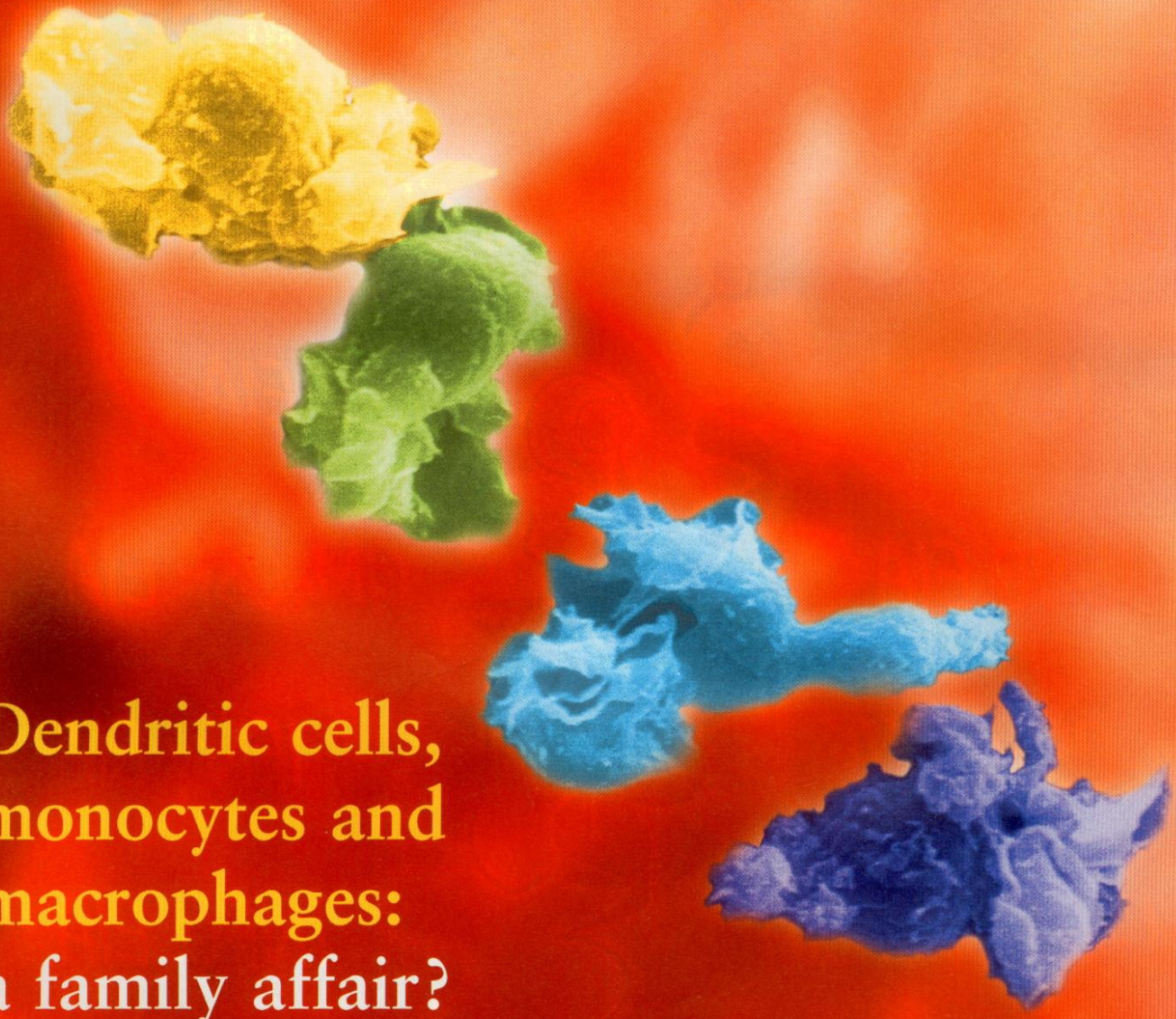

Dendritic cells, monocytes and macrophages: a family affair?

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Dendritic cells: from ontogenetic orphans to myelomonocytic descendants

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Although dendritic cells (DCs) and macrophages share a bone marrow origin, these cells were long assumed to differentiate via discrete pathways. DCs have now been clearly shown to develop from myeloid lineage precursors, and recent evidence suggests that they may even differentiate from blood monocytes. Here, J. Hinrich Peters and colleagues assess current knowledge on the myelomonocytic origin and successive differentiation of human T-cell-directed DCs.

Antigen-presenting cells (APCs) serve as an immunological window to the foreign world. In general, the various types of APC can be divided into professional and nonprofessional cells. While the latter are found among nonlymphoid cells, professional APCs, such as dendritic cells (DCs), macrophages (Mϕs) and B cells, form an integral part of the immune system. However, although they show common characteristics in their ability to ingest, process and present antigens, these cells serve very different immune functions. DCs are the most potent initiators of the immune response and, in particular, are responsible for the induction of primary antigen-specific immune reactions. This implies that these cells are fundamental to intact immunity and antigen specificity in general.

DCs are sparsely distributed in the tissues and, hence, are difficult to isolate. Moreover, the epigenetic potential of DC precursors enables them to express discrete, though overlapping, features within the different tissues. Since DCs change in phenotype during their lifespan and thus do not carry stable markers, it is difficult to pinpoint individual phenotypes clearly within the huge family of DCs or even to use certain markers for ontogenetic deductions. Furthermore, several DC functions, including the induction of secondary immune responses, can partially be substituted for by Mϕs and other APCs. As a consequence, DCs are only on the threshold of being well-defined immune cells. It is likely that this unsatisfactory situation could be improved if the ontogeny of this class of cells was elucidated.

The question of whether DCs originate from a separate lineage or belong to the monocyte/macrophage (MO/Mϕ) family is still unresolved – in other words, the DC family tree has not yet been drawn. Recently, it was shown that a discrete DC colony-forming unit (CFU-DC) can be generated *in vitro* and evidently exists in the bone marrow[1]. Nevertheless, it has been clearly demonstrated that DCs can also differentiate from myeloid precursors[2] and human peripheral blood MOs (see below). Moreover, the disruption of DC differentiation has been found to lead to enhanced production of Mϕs and neutrophils[3], which indicates a compensatory mechanism and supports the concept of a common lineage of DCs and Mϕs. Hence, DCs and Mϕs may be considered as polar representatives of one common regulatory system.

Mϕs and DCs as offspring from separate lineages?

Mϕs were originally regarded as the principal APC population. This notion resulted from the initial work on APCs, carried out on Mϕs (Ref. 4), which found that accessory activity was lost on treatment with the phagocytotoxic agent L-leucine methyl ester[5].

Phagocytic activity was considered a hallmark of all myelomonocytic offspring[6,7]. Conversely, cells lacking this classical MO/Mϕ feature were, by definition, excluded from the possibility of belonging to the mononuclear phagocyte system (MPS). As a consequence of these early studies, DCs were long assumed to descend from a separate lineage[8–10]. However, time has turned this initially well-reasoned working hypothesis into a dogma, which is now being increasingly refuted.

Myeloid origin of DCs

Similar to all other $CD45^+$ cells, DCs derive unequivocally from bone marrow precursors. This was first shown for epidermal Langerhans cells (LCs), when allogeneic bone marrow transplantation led to donor-strain-specific expression of major histocompatibility complex (MHC) class II molecules in the skin[11,12]. Studies in mice showed LCs to be precursors of DCs (Ref. 13) and, in common with mouse MO/Mϕs, LCs express the MPS marker F4/80 (Ref. 14). Wood and co-workers showed that human MO/Mϕ and DC subsets share the same MHC class II, $L3B12^+$, $CD14^+$, $CD4^+$ phenotype and suggested that 'macrophages and dendritic cells are more closely related to one another than to other leukocyte subsets'[15].

In another early attempt to shed light on the origin of DCs, human bone marrow colonies grown from single cells were shown to contain MO/Mϕs and DCs, which again indicated their common

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Table 1. Inducers used to convert human myeloid cells into dendritic cells

Source	Starting population	Cytokine or inducer	Resulting phenotype	Functional activites	Refs
Blood	MO	None (serum free)	Veiled cell	Allogeneic T-cell stimulation $^{+}$	24
Blood	MO	Iodine compounds	MOAC/veiled cell	MLR $^{++}$	42
Blood	MO-derived Mϕ	Cyclic AMP	MϕAC	Allogeneic T-cell stimulation $^{++}$	32
Blood	MO	Adenosine nucleotides	MOAC	Allogeneic T-cell stimulation $^{+}$	56
Blood	MO	IL-1 and IL-6	Indeterminate MO/MOAC	Allogeneic T-cell stimulation $^{+}$	57
Blood	MO	3% FCS	MOAC/LC-like cell ($CD1a^{+}/CD14^{-}$)	Phagocytosis low, MLR $^{+}$	25, 26
Blood	MO	IL-4 and GM-CSF	AC ($CD1a^{+}$)	Mycobacterium-specific-T-cell proliferation	37
Blood	MO	IL-4 and IFN-γ	DC ($CD14^{+}$)	MLR $^{+}$	58
Blood	MO	IL-4 and GM-CSF	DC ($CD14^{-}$)	MLR $^{+}$	36
Blood	MO	IL-4 and GM-CSF	MODC	MLR $^{++}$	28
Blood	MO	IL-4, GM-CSF and IFN-γ	MODC	Phagocytosis $^{-}$, MLR $^{++}$	40
Cord blood	$CD34^{+}$ cell	TNF-α and GM-CSF	DC	MLR^{++}	20
Cord blood	$CD34^{+}$ cell	TNF-α, GM-CSF and CD40L	DC	MLR^{++}	23
Bone marrow (rat)	Nucleated bone marrow cell	IL-3 (low), M-CSF (low), linoleic acid, α-tocopherol and cholecalciferol	DC	Allogeneic T-cell stimulation $^{+}$, phagocytosis $^{-}$	17
Bone marrow	$CD34^{+}$ cell	TNF-α, GM-CSF and IL-3	DC	ND	2
Bone marrow	$CD34^{+}$ cell	TNF-α, GM-CSF and SCF	DC	Phagocytosis $^{-}$, MLR	22
Blood	$CD33^{+}/CD14^{dim}$ cell	None	DC	MLR $^{+}$	44
Blood	Adherent cell (MO)	IL-4 and GM-CSF	DC	MLR $^{++}$	39
Blood	PBMC	IL-4 and GM-CSF	DC	MLR $^{++}$	38

Abbreviations: AC, accessory cell; CD40L, CD40 ligand; DC, dendritic cell; FCS, fetal calf serum; GM-CSF, granulocyte–macrophage colony-stimulating factor; IFN-γ, interferon γ; IL-1, interleukin 1; LC, Langerhans cell; Mϕ, macrophage; MϕAC, macrophage-derived accessory cell; M-CSF, macrophage colony-stimulating factor; MLR, mixed leukocyte reaction; MO, monocyte; MOAC, monocyte-derived accessory cell; MODC, monocyte-derived dendritic cell; ND, not determined; PBMC, peripheral blood mononuclear cells; SCF, stem-cell factor; TNF-α, tumour necrosis factor α; −, negative; +, ++, positive of graded intensity.

myeloid origin[16]. However, the precise point at which DCs differentiated from the myelomonocytic lineage remained unclear. It was subsequently shown using rat bone marrow cells that DCs, but not Mϕs, could be induced to develop from myeloid clones after having passed through the MO stage[17,18]. Similar studies with human bone marrow cells showed that the differentiation of $CD14^{+}$ (pro-) monocytes, which coexpressed the LC marker CD1 (Ref. 19), and propagation of clones from single $CD34^{+}$ bone marrow precursors gave rise to a spectrum of Mϕs and DCs ($CD1a^{+}$ or $CD1a^{-}$)[2]. These findings, together with further studies[20–23], clearly showed that LC-like cells, as well as other DCs, can indeed be induced from myeloid precursors.

DCs as derivatives of monocytes

Although in 1987 it was still commonly acknowledged 'that macrophages and dendritic cells have never been observed to interconvert'[9], it was shown in the same year that human nonproliferating blood MOs could be differentiated into cells expressing DC characteristics. In the presence of human serum, these MO-derived accessory cells (MOACs) developed into Mϕs (Ref. 24). This line of evidence favours a basic myeloid differentiation programme leading from early progenitors, via blood MOs, to an early indeterminate MOAC type (Table 1; Fig. 1) that can develop further into either a DC or a Mϕ.

Additional evidence for a monocytic origin of DCs arose from the differentiation of peripheral blood MOs into $CD1a^{+}$ ACs *in vitro*[25].

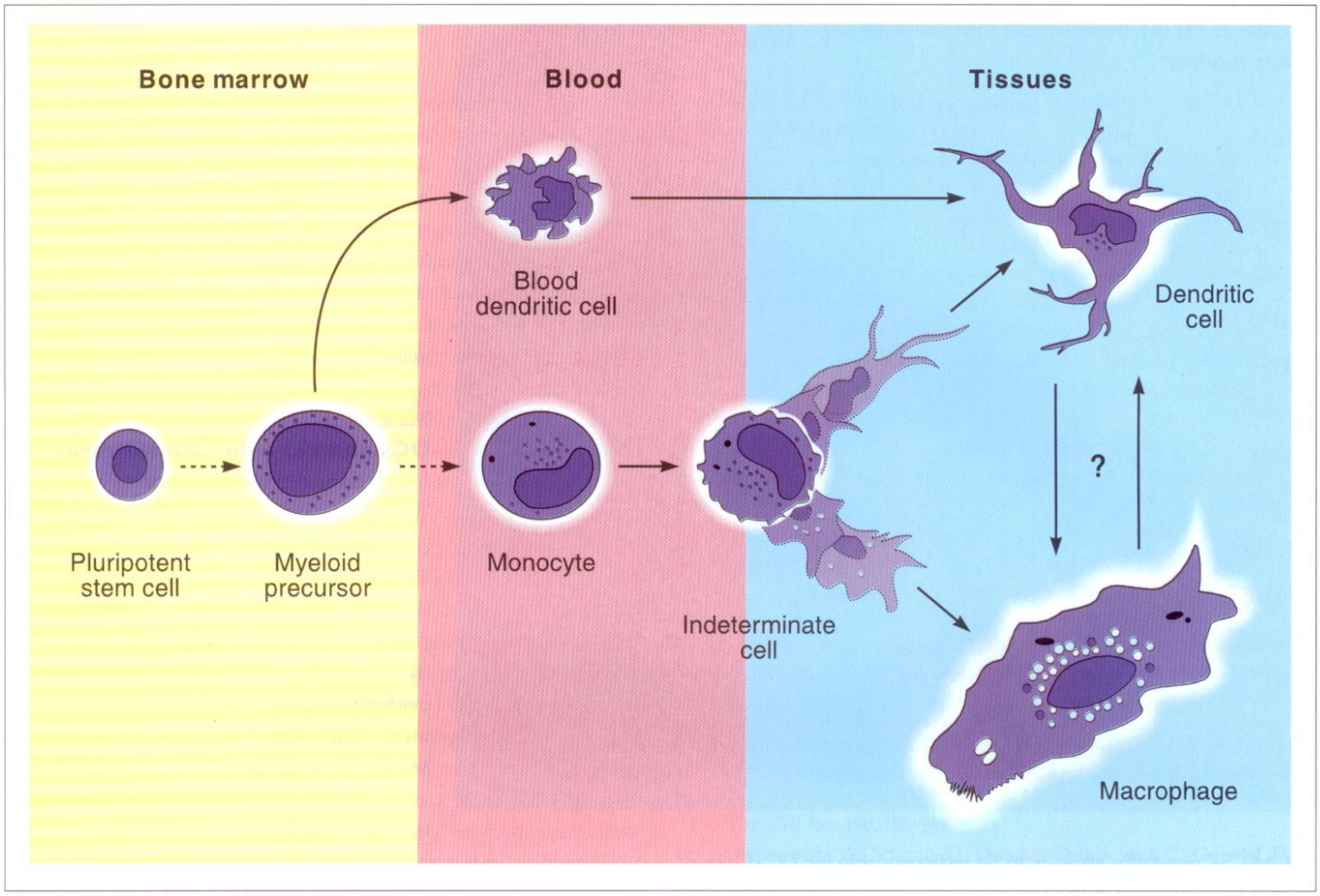

Fig. 1. *Two possible pathways of dendritic cell (DC) development. DCs derive from a myeloid precursor that is common to the monocyte/macrophage (MO/Mϕ) developmental pathway. DCs might branch off early within this lineage and then appear in the blood as an immature-type DC, which completes its differentiation after entering a tissue (upper pathway). Alternatively, DCs and MO/Mϕs may develop from a late monocyte (lower pathway) termed the indeterminate cell, which is characterized by weak adherence and weak expression of nonspecific-esterase, Fc receptors and weak phagocytosis. Broken arrows indicate that some cell stages have been omitted. The possible interconversion between DCs and Mϕs is still an open question.*

Since such cells downregulated CD14 in parallel, they represented MOACs of an LC-like phenotype, which could already stimulate an allogeneic mixed leukocyte reaction (MLR)[26]: a functional capacity attributed to DCs.

It must be pointed out that a number of experiments were performed to rule out the possibility that MO preparations contained $CD34^+$ cells, which potentially could outgrow and give rise to DCs. Such contaminants were generally <1%, and proliferation was generally not detected. At a continuous viability of >95%, no significant increase in cell number was observed[25,26]. Furthermore, MOACs and MO-derived DCs (MODCs) were generated in >95% of the experiments performed with healthy donor cells, thus leading to populations of monocytic cells of which >95% expressed the accessory phenotype[25,27,28]. These data demonstrate that MOs ($CD14^+$, adherent, nonspecific-esterase$^+$ cells) and no other contaminating populations serve as DC precursors.

All of this evidence strongly suggests that DCs may branch off from the myelomonocytic lineage soon after the MO differentiation state (Fig. 1). This contention was further supported by the finding that MO-derived Mϕs reveal a transient state of high accessory activity and low expression of Mϕ markers before assuming classical Mϕ characteristics[17,24,29,30]. Moreover, evidence exists showing that even mature Mϕs may convert into potent DCs (Fig. 1), if signals causing an increase in intracytoplasmic cyclic AMP are provided[31].

Signals for DC differentiation

In searching for the stimuli required for DC differentiation, several scientists have established myelomonocytic culture systems from which DCs can be derived (Table 1). A variety of lessons were learned from using early $CD34^+$ stem cells as the starting population and later from employing MOs. Such stem cells, grown in the presence of tumour necrosis factor α (TNF-α) and granulocyte–macrophage colony-stimulating factor (GM-CSF), gave rise to $CD14^{dim}$ cells, partially expressing Birbeck granules, which are typical of LCs (Ref. 20). After prolonged culture, stem-cell-derived DCs lost their typical morphology and the colonies comprised Mϕs and dendritiform cells, which again indicated that DCs represent a transient state within MO/Mϕ differentiation[21]. Recent results show that stem-cell factor (SCF) enhances proliferation of the mixed CFU-DC/MO or the pure CFU-DC (Refs 1, 22), and that DC maturation might continue until DC–T-cell interactions occur[23]; this is due to crosslinking of CD40 which upregulates expression of the co-stimulatory molecules CD80 and CD86.

Table 2. Major phenotypic markers of selected antigen-presenting cells *in vitro*[a]

Marker	MO	Indeterminate cell/MOAC	MODC	LC (skin)	Mϕ
CD1	−	+	++	+ to ++	−
CD14	+++	++	− or +	−	+ to +++
CD33	+	(+)	(+)	(+)	− to ++
CD40	+	++	+++	+++	+
CD64	+	−	−	−	+
CD80	−	−	+	+	+
CD86	− or +	+	++	++	− or +
HLA-DR	+	++	+++	+++	+
HLA-DP	−	+	++	++	−
HLA-DQ	−	+	++	++	−

Abbreviations: LC, Langerhans cell; MO, monocyte; Mϕ, macrophage; MOAC, monocyte-derived accessory cell; MODC, monocyte-derived dendritic cell. −, negative; (+), weakly positive; +, ++, +++, positive of graded intensity.
[a]This table does not include all subpopulations of antigen-presenting cells (APCs) that have been described, or refer to the enormous heterogeneity of subpopulations observed *in vivo*. It concentrates on markers that are involved in regulation and that underline the close relationship of the different cell types.

GM-CSF generally appears to be indispensable for DC differentiation: MOs cultured in the presence of this factor upregulate CD1a (Ref. 32). The incubation of MOs with interleukin 4 (IL-4) causes the downregulation of CD14 (Refs 33–35) – an effect that might be achieved under serum-free conditions by using both IL-4 and GM-CSF (Ref. 36). Incubation of MOs with GM-CSF and IL-4 leads to the production of ACs that potently stimulate the proliferation of T cells specific to mycobacteria[37]. Complete differentiation of DCs can eventually be achieved when peripheral blood monocuclear cells[38], adherent blood cells[39] or MOs (Ref. 28) are incubated in culture media containing IL-4, GM-CSF, serum and/or endogenous factors. In addition, other signals, such as interferon γ (IFN-γ) (which upregulates expression of MHC class II) might synergize with IL-4 and GM-CSF to enhance the generation and functional potency of MODCs (Ref. 40).

DC precursors in the peripheral blood

Blood DCs are usually characterized only after being subjected to stressful purification procedures, which may supply unknown differentiation stimuli. Early observations based on alternative purification methods[41,42] that yielded higher numbers of veiled cells in the human peripheral blood, may point towards a more plastic population of DC precursors, including MOs. However, the presence of a more immature type of DC in the blood might represent newly generated DCs (Ref. 43) that originate from the proposed CFU-DC in the bone marrow[1] and traffic towards the periphery. This indicates that the differentiation of DCs involves at least two pathways: branching off either from an early bone marrow precursor or later at the post-monocytic level (Fig. 1).

When comparing peripheral blood DCs with MOs, $CD14^{dim}/CD33^{+}$ cells were classified as DC precursors[44]. Nevertheless, the assumption that CD14 is an irreversible marker of terminally differentiated MO/Mϕs requires re-evaluation, since CD14 is subject to IL-4 regulation (see above) and $CD14^{-}$ (or slightly $CD14^{+}$) cells may also develop from a post-monocytic state (Table 2).

DCs and Mϕs: dichotomic offspring from monocytic parents

To what extent do monocytic offspring derive from, or interconvert into, one another? To understand this, it is important to consider the variable marker compositions expressed within the members of the DC family. Expression of markers and functions evidently depends upon the microenvironment and the stage of development. Moreover, as methods for identifying markers become more sensitive, those that have been previously reported as negative have subsequently been found expressed on DCs. Examples include complement receptors[14,45], acid phosphatase and nonspecific-esterase[1,9] (R. Gieseler, PhD Thesis, Georg-August University, 1987). Human CD68, rat ED1 and mouse MOMA-2, once regarded as constitutive markers of tissue Mϕs, have been demonstrated in DCs (Ref. 46). LCs of the nasal-associated lymphoid tissue were even reported to coexpress CD14 and CD1a (Ref. 47).

Fluctuating accessory activity was found to depend on the environment: for example, overnight culture of lung DCs increased their accessory activity, while soluble factors from Mϕs suppressed it[48]. Phagocytosis, the central feature of the MO/Mϕ system, is also found in some stages of DC differentiation. Although LCs were shown to be generally phagocytic[49,50], the most recent description of macropinocytosis and the use of the mannosyl fucosyl receptor (MFR) by human DCs (Ref. 51) not only underlines the endocytic capacity of DCs (Ref. 52), but also supports a myelomonocytic origin of DCs as the MFR has only been shown on monocytic cells[53].

Together, these data reinforce the view that it would be unwise to construct an 'ideal DC': no single characteristic, but rather a 'bundle' of criteria that cover different features must be taken as evidence of a cellular status. Certain characteristics are rarely exclusive to one given cell. Hence, rather than relying on evidence based on single markers, it would be better to construct an analytical framework comprising several phenotypical and functional characteristics; cells must then fit into this framework, without being obliged to incorporate all the features within it. However, myeloid cells must not carry key markers that are indicative of nonmyeloid lineages. Despite the present lack of a commonly accepted nomenclature for DCs, criteria that can be used to define DCs *in vitro* include: the expression of CD1a; accessory markers such as CD40, CD80, CD86

and MHC class II; as well as the ability to stimulate proliferation of allogeneic T cells in an MLR. These criteria are also met by MODCs (Refs 28, 40) (Table 2).

More general markers that describe the state of maturation of cells have also been identified. The nuclear membrane contains different kinds of lamins that characterize immature and mature cells. DCs, as well as Mϕs (differentiated from the same precursors), express A/C lamins, while the MOs in culture are only positive for lamin B, which is characteristic of immature cells[18]. This suggests that the MO is a relatively immature precursor cell (see Fig. 1), which may terminally differentiate into either a DC or Mϕ, depending on the stimuli provided.

Implications

The transition from MOs to DCs can be induced under physiological conditions *in vitro*. Thus, similar regulatory events may take place *in vivo*, giving rise to the many variations among DCs and Mϕs observed at different sites, as a consequence of different functional demands, and at different stages of maturation. This strongly suggests that plurality is the rule rather than the exception. Plurality may comprise an early debranching of DCs from a CFU-DC (Ref. 1) as well as a late debranching from the monocytic level. The apparent continuum between DCs and Mϕs should thus be regarded as a basic phenomenon that has a broad impact on our understanding of the microenvironmentally directed development of tissue-specific DCs.

The ability to prepare significant numbers of pure, unstimulated DCs is likely to provide a novel and promising approach in the treatment of immunologically relevant disorders. Accordingly, the concept of developmental plasticity not only has widespread implications for understanding immune defence and tolerance induction[54], but also promises to be of increasing value for future therapeutic applications[55].

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