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Human dendritic cell subsets

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Summary

Dendritic cells are highly adapted to their role of presenting antigen and directing immune responses. Developmental studies indicate that DCs originate independently from monocytes and tissue macrophages. Emerging evidence also suggests that distinct subsets of DCs have intrinsic differences that lead to functional specialisation in the generation of immunity. Comparative studies are now allowing many of these properties to be more fully understood in the context of human immunology.

Keywords: dendritic cells; haematology; therapy/immunotherapy.

Introduction

The orchestration of effective immunity in vertebrates depends upon dendritic cells (DCs), a class of bone-marrow-derived cells found in the blood, epithelia and lymphoid tissues. DCs are equipped with molecular sensors and antigen-processing machinery to recognize pathogens, integrate chemical information and guide the specificity, magnitude and polarity of immune responses. Recent advances have helped to define DCs as a distinct haematopoietic lineage and to establish functional specialization between different DC subsets. The aim of this review is to present a coherent framework for understanding human DC subsets and their functional roles *in vivo*.

How are DCs distinct from monocytes and macrophages?

Dendritic cells, monocytes and macrophages traditionally comprise the mononuclear phagocyte system. An emerging theme is that components of this system are not as related as was presumed a decade ago. The phenotypic differences between human DCs and macrophages are discernible by immunohistochemistry[1,2] and a clear functional distinction is the ability of DCs to leave tissues while macrophages remain fixed. This property may be tested directly by explanting tissue *in vitro*, and is mirrored by significant differences in turnover between DCs and macrophages after stem cell transplantation *in vivo*.[3]

More recently, the taxonomy of DC populations and their homology to mouse DC subsets have been scrutinized by transcriptional profiling.[4–11] This has been assisted by a large and systematic effort to profile human and mouse leucocytes (Biogps; Immgen, www.biogps.org, www.immgen.org).[12,13] Principal component analysis conveniently displays multidimensional data in a format familiar to flow cytometrists and reveals that quiescent primary DCs form discrete populations separate from monocytes (Fig. 1). This accords with ontogenetic studies in mice showing that most steady-state DCs are derived from committed DC-restricted precursors independently of monocytes.[14]

The power of this approach is that it offers an unbiased assessment of relationships between cells rather than reliance upon a small selection of markers. The pitfalls in relation to DC lineage studies are that hierarchical clustering and principal component analysis are exquisitely sensitive to tissue-specific effects arising during preparation; this can easily obscure the relationships between similar DCs isolated from different sources. These effects can be minimized by bioinformatic strategies based on gene set enrichment analysis in which subset-specific signatures are identified or tissue-specific gene sets are removed before analysis. Most tissue-specific effects are the result of different states of maturation. It has recently been shown that strong activating stimuli induce convergence of DC transcriptional profiles through nuclear factor-κB and interferon-inducible pathways and naturally tend to obscure ontogenetic differences in transcriptional profiles.[15]

Overview of human dendritic cell lineages

Recent comparative phenotypic and functional studies have delineated a small number of distinct DC subsets

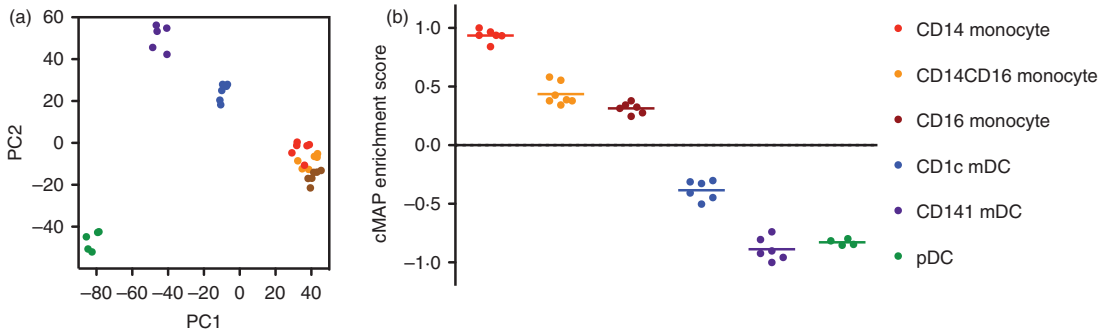

Figure 1. Transcriptional profiling of blood monocytes and dendritic cells (DCs). (a) Principal component analysis; (b) Connectivity mapping (cMAP) of gene set enrichment. The prinicipal components (PCs) are vectors that account for most of the variability in the populations and illustrate the clustering of all monocyte populations separately from DCs. Plasmacytoid DCs have the most distinct DC signature and cluster away from the two myeloid DCs and the monocyte cluster. The percentage variation accounted for by PC1 and PC2 in the example shown is 32·6% and 13·7%, respectively. Connectivity mapping defines the enrichment of different populations for a given gene signature. The cMAP enrichment score is a scalar quantity normalized to the index gene signature. The example shows the enrichment of monocyte and DC transcriptional profiles for the CD14 monocyte signature, illustrating the relatedness of all monocyte populations, intermediate status of $CD1c^+$ DCs and distant relationship of $CD141^+$ DCs and pDCs. The gene signature of each population is defined by those genes whose expression exceeds an average obtained from all the other populations. Each point represents a biological replicate ($n = 6$). Data replotted from ref. 8 courtesy of Pavandip Wasan, Michael Poidinger and Florent Ginhoux (Singapore Immunology Network).

that are widely distributed in all mammals (Table 1). In humans, all DCs express high levels of MHC class II (HLA-DR) and lack typical lineage markers CD3 (T cell), CD19/20 (B cell) and CD56 (natural killer cell). The classical descriptions of DCs as $HLA\text{-}DR^+$ $lineage^-$ cells have been refined to include a number of positive DC lineage markers that identify DCs as either 'myeloid' or 'plasmacytoid' according to recent convention.[16]

Myeloid DCs (mDCs)

Myeloid DCs (mDCs) express typical myeloid antigens CD11c, CD13, CD33 and CD11b, corresponding to mouse $CD11c^+$ 'classical' or 'conventional' DCs. In humans both monocytes and mDCs express CD11c, but DCs lack CD14 or CD16 and may be split into $CD1c^+$ and $CD141^+$ fractions. These two fractions share homology with mouse classical DCs expressing either CD11b ($CD1c^+$ DCs) or CD8/CD103 ($CD141^+$ DCs).

Plasmacytoid DCs (pDCs)

Plasmacytoid DCs (pDCs) typically lack myeloid antigens and are distinguished by expression of CD123, CD303 and CD304. Although not related directly to plasma cells they retain subtle lymphoid features and unique secretory properties. Homologues are recognized in many species.

$CD14^+$ DCs

$CD14^+$ DCs found in tissues and lymph nodes are a third subset of $CD11c^+$ myeloid cells originally described as 'interstitial DCs'. They are more monocyte-like or macrophage-like than $CD1c^+$ and $CD141^+$ mDCs and may arise from classical monocytes. Equivalent cells have recently been found in mice as a new monocyte-derived subset of CD11b classical DCs that expresses or ESAM.

Langerhans cells (LCs) and microglia

Langerhans cells (LCs) and microglia are two specialized self-renewing DC populations found in stratified squamous epithelium and parenchyma of the brain, respectively. The LCs are capable of differentiating into migratory DCs whereas microglia are considered as a type of macrophage by many authors. Recent reviews provide excellent summaries of microglia and they will not be discussed further.[17]

Functional–anatomical classification of dendritic cells

A functional–anatomical classification derived from murine studies recognizes that DC function is intimately linked to location.[18] Primarily this separates 'migratory' DCs that have trafficked through the tissues, from 'resident' DCs that arise in lymph nodes directly from the blood. Two further compartments also merit consideration: blood DCs and inflammatory DCs. The distribution of human DC subsets is summarized in Fig. 2.

Blood/precursor DCs

Blood DCs are well defined in humans, and are likely to be precursors of tissue and lymphoid organ DCs. In support of this, blood contains pDCs, $CD1c^+$ and $CD141^+$ mDCs in immature forms of those found in tissues and lymph

Table 1. Human mouse homology.

	Human	Mouse	Refs
Myeloid/Classical			
Major subset 	CD1c$^+$ *Dectin 1 (CLEC 7A)* *Dectin 2 (CLEC6A)*	CD11b$^+$ (tissues) CD4$^+$ CD11b$^+$ (lymphoid) *ESAM*	(8, 10, 11, 82, 83)
Cross-presenting 	CD141$^+$ *CLEC9A* *XCR1*	CD103$^+$ (tissues) CD8$^+$ (lymphoid) *CLEC9A* *XCR1* *Langerin*	(8, 35, 37, 40, 41, 54)
Plasmacytoid 	*CD303 (CLEC4C)* *CD304 (neuropilin)* *CD123 (IL-3R)*	*B220* *Siglec H*	(5, 6, 19, 20, 57)
Monocyte-related 	CD14$^+$ DC *CD209 (DC-SIGN)* *Factor XIIIA*	CD11b$^+$ CD64$^+$ tissue DC *CX3CR1* *CD14*	(3, 56, 75, 76)
	CD16+ monocyte *CX3CR1^{hi}* *SLAN (subset)*	Gr-1/Ly6C low monocyte *CX3CR1^{hi}* *CCR2 negative*	(20, 84, 85)
	Inflammatory DC *CD1c* *CD16 negative*	Monocyte-derived DC *CD209 (DC-SIGN)* *CD206*	(9, 53, 81, 82, 83, 84)

Surface markers of the major human DC populations and their murine homologues. Myeloid DCs and mouse classical DCs (also known as conventional DCs) contain a major subset and a minor specialised cross-presenting subset. Plasmacytoid DCs are easily recognisable in many species. Monocyte related DCs include a recently recognised subset of CD11b+ DCs that may be homologous to human CD14+ DCs. Inflammatory monocyte-derived DCs are also recognised in both species but are heterogeneous.

nodes.[19,20] Mice also have blood pDCs and circulating precursors of classical DCs known as pre-cDCs. Pre-cDCs are blood mDCs in all but name and comprise multiple subsets that may correspond to the two human myeloid blood DCs.[21]

Non-lymphoid/tissue/migratory DCs

Most epithelial tissues contain 'non-lymphoid' or 'migratory' DCs whose function is to acquire antigen and migrate via the afferent lymphatics to lymph nodes. Quiescent interstitial tissues contain CD1c$^+$ mDCs, CD141$^+$ mDCs and CD14$^+$ DCs but few pDCs.[8,22] Epidermal LCs also migrate to form a component of afferent lymphatic DCs[23] but it remains uncertain whether CD14$^+$ DCs are migratory.[24]

Lymphoid/resident DCs

Lymphoid tissue also contains a large cohort of blood-derived non-migratory 'lymphoid' or 'resident' DCs. In the steady state, these may be difficult to separate from migratory DCs derived from the tissues. Human lymphoid tissue is less well described than mouse but contains CD1c$^+$ mDCs, CD141$^+$ mDCs and pDC in the steady state, in addition to a number of CD14$^+$ populations.[8,22] The contingent of resident lymphoid and migratory DCs in lymph nodes increases markedly during inflammation.

Inflammatory DCs

The content of tissues and lymphoid organs is dramatically altered during inflammation principally by the recruitment of granulocytes, classical monocytes and pDCs. Steady-state DC populations become more difficult to detect either because they migrate or are diluted by recruited cells. CD14$^+$ classical monocytes are the putative precursors of inflammatory DCs. It is not known whether blood DCs are also recruited during inflammation but expression of CD62L and CXCR3, (receptor for interferon-γ-inducible chemokines CXCL9,10,11) suggests that they are competent to extravasate. Recent work confirms that inflammatory exudates contain two populations with polarized DC and macrophage properties.[9] The relative contributions of migrating tissue DCs and newly recruited inflammatory DCs to the initiation of immunity, is a critical unresolved problem in humans.

CD1c$^+$ myeloid DCs

CD1c$^+$ mDCs are the major population of human mDCs in blood, tissues and lymphoid organs. They were originally recognized in the blood as a fraction of HLA-DR$^+$ lineage$^-$ cells expressing myeloid antigens CD11b, CD11c, CD13, CD33, CD172 (SIRPa) and CD45RO[25] and

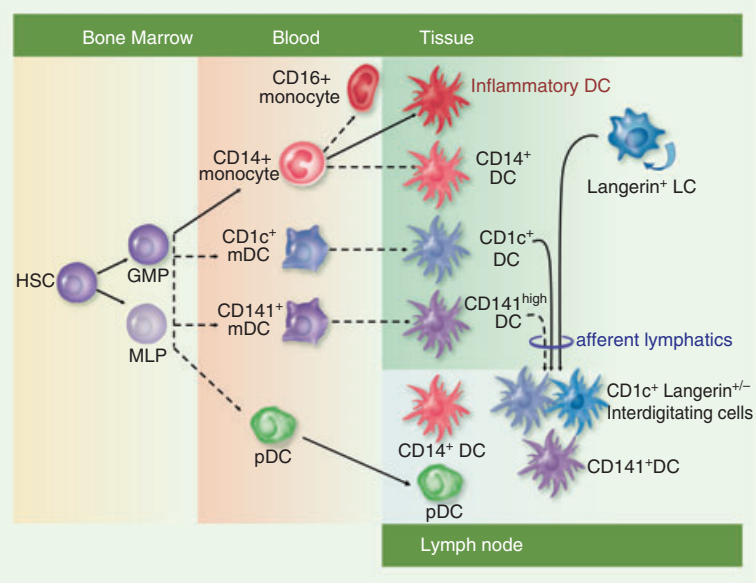

Figure 2. The distribution of major human dendritic cell (DC) subsets in blood, epithelial tissues and lymph nodes. Broken arrows indicate relationships that require further confirmation in humans. Human DCs can be generated either from granulocyte–macrophage progenitors (GMP) or multi-lymphoid progenitors (MLP) both of which ultimately arise from haematopoietic stem cells (HSC). Classical monocytes, blood myeloid DC (mDC) and plasmacytoid DC (pDC) are putative precursors of tissue and lymphoid DCs. Non-classical monocytes are reported to arise by conversion of classical monocytes in the mouse. Inflammatory DCs and $CD14^+$ DCs have transcriptional profiles suggesting that they arise from monocytes; likewise tissue $CD1c^+$ DCs and $CD141^+$ DCs are related to their blood counterparts. Myeloid DCs and Langerhans cells (LCs) both form interdigitating cells in skin-draining lymph nodes. $CD14^+$ DCs and pDCS are also found in nodes but may arise directly from the blood rather than by migration from tissues.

comprise approximately 1% of mononuclear cells, usually slightly lower than pDCs. CD1c was identified as a useful marker by the commercial antibody BDCA-1.[19]

In tissues, dermal $CD1c^+$ DCs were originally described as the $HLA\text{-}DR^+$ 'indeterminate' cell by electron microscopy (EM)[26] and later characterized as $CD1a^+$ DCs migrating from *in vitro* explants.[27,28] Although dermal $CD1c^+$ DCs and LCs both express CD1a, LCs may be identified by Langerin, epithelial cell adhesion molecule (EpCAM) and higher CD1a expression.[1,3,29]

Human tissue $CD1c^+$ DCs appear more activated than their blood counterparts in terms of expression of CD80, CD83, CD86 and CD40. They have lost expression of homing receptors CLA and CD62L but up-regulated CCR7.[1,29,30] A potential precursor–progeny relationship between blood and tissue $CD1c^+$ DCs is supported by recent *in vitro* differentiation and gene expression analysis.[8] This model is not universally accepted on the grounds that simple hierarchical clustering fails to discern any lineage relationship between blood and skin.[11]

In lymph nodes, $CD1c^+$ DCs are found as 'interdigitating cells' of T-cell areas. Variable expression of CD1a and Langerin in skin-draining nodes suggests that both $CD1c^+$ DCs and LCs contribute to this population.[31–33] Tonsil and spleen also contain $CD1c^+$ DCs.[34–36] As these tissues do not receive afferent lymph, it is concluded that some $CD1c^+$ DCs are 'resident DCs' originating directly from the blood.[8,37]

$CD1c^+$ DCs are equipped with a wide range of lectins, toll-like receptors (TLRs) and other pattern recognition receptors for general purpose antigen uptake, transport and presentation. Through TLRs 1–8 they respond well to lipopolysaccharide, flagellin, poly(IC) and R848.[38] The potential of CD1c and CD1a to present the glycolipid antigens of mycobacteria and other pathogens is often overlooked.[39] Dectin-1 (CLEC7A) and Dectin-2 (CLEC6A) are highly expressed, suggesting a role in fungal recognition.[10,11] DEC205 (CD205; CLEC13B) and macrophage mannose receptor (CD206; CLEC13D) are variable.[22] $CD1c^+$ DCs are good stimulators of naive CD4 T cells but have inferior capacity to cross-present antigen to CD8 T cells compared with $CD141^+$ DCs.[8,35,37,40,41] They secrete tumour necrosis factor-α (TNF-α), interleukin-8 (IL-8) and IL-10 when stimulated and produce IL-12 in response to TLR7/8 ligation by R848.[36] A small amount of IL-23 can be detected after a range of stimuli.[42] This implies a dual role in T helper type 1 (Th1) and Th17 sensitization and highlights the plasticity of DCs in different contexts. Deletion of the equivalent CD11b DC subset of mice leads to a range of functional deficits in Th1, Th2 and Th17 immunity (reviewed in ref. 43).[102]

CD141^{high} myeloid dendritic cells

The expression of CD141 or thrombomodulin on approximately 10% of human blood mDCs (0·1% of mononuclear cells) was noted over a decade ago with the development of the blood DC antibody BDCA-3.[19,20] CD141$^+$ DCs have also been found among resident DCs of lymph node, tonsil, spleen and bone marrow[22,35–37] and non-lymphoid tissues, skin, lung and liver.[8]

CD141$^+$ DCs are difficult to identify *in situ* owing to their small numbers and the wide expression of CD141 on other cells.[37] In particular, CD141 is found on migratory CD14$^+$ DCs and on CD1c$^+$ DCs and monocytes cultured with vitamin D.[44] Differentiation from the major CD1c$^+$ DC subset by flow cytometry is aided by the observation that CD141$^+$ DCs express less CD11b and CD11c.[8,45]

The realisation that human CD141$^+$ DCs are homologous to mouse CD8$^+$ lymph node DCs[35,37,40,41] and CD103$^+$ tissue DCs[8] is something of a Rosetta stone in DC biology, enabling the systematic alignment of human and mouse DC subsets across lymphoid and non-lymphoid tissues. Both CD141$^+$ and CD8$^+$ DCs have acquired the status of 'cross-presenting' DCs in comparison with other myeloid or classical DCs.[46] Comparative biology approaches have also identified CLEC9A,[47–49] XCR1,[50] Necl2[51] and TRL3 expression[52] as a concise functional profile that species barriers. DEC205, a marker of CD8$^+$ mouse DCs, is not restricted to human CD141$^+$ DCs but XCR1 and CLEC9A have emerged as universal markers of cross-presenting DCs in multiple species.[45,50]

CD141$^+$ mDCs have an enhanced ability to take up dead or necrotic cells via CLEC9A,[40,49] sense viral nucleic acids with TLR3 and TLR8 and to cross-present antigen to CD8$^+$ T-cell clones *in vitro*.[8,35,37,40] This function is consistent with their homology to mouse CD8$^+$/CD103$^+$ DCs, although CD141$^+$ DCs show less enrichment for gene transcripts controlling class I presentation than the homologous mouse DCs.[6] CD141$^+$ DCs readily secrete TNF-α, CXCL10 and interferon-λ but surprisingly little IL-12 p70, in contrast to mDCs and CD1c$^+$ DCs.[8,36,53,54] Notably, other populations of human DCs derived *in vitro* are also capable of cross-presentation, especially LC-like cells differentiated in granulocyte–macrophage colony-stimulating factor (GM-CSF) and TNF-α.[55,56] Overall, the division of labour between CD141$^+$ DCs and other myeloid DCs appears less sharply demarcated than in the mouse, a reminder that functional cross-species comparison is an imprecise science.

Plasmacytoid dendritic cells

Plasmacytoid DCs have unique specialized functions that have been extensively reviewed.[57] The most numerous blood DCs, they lack myeloid antigens CD11b, CD11c, CD13 and CD33 but express CD45RA, variable CD2 and CD7 and may harbour T-cell receptor and immunoglobulin rearrangements. The morphological epithet ' plasmacytoid' reflects abundant secretory capacity and avoids the anatomical connotations of 'lymphoid'. Plasmacytoid DCs are now separable from mDCs by positive markers CD123 (IL-3R), CD303 (CLEC4C; BDCA-2) and CD304 (neuropilin; BDCA-4).[19] They are not abundant in quiescent tissues but are present in LN at about 20% of MHC class II positive cells and are rapidly recruited to both sites in inflammation.[58]

The propensity of pDCs to release type 1 interferon in response to viruses was one of the first specialized DC functions to be described.[59–61] They express very high levels of TLR7 and TLR9, which transduce signals from viral and self nucleic acids.[62,63] Freshly isolated blood pDCs do not prime naive T cells efficiently and appear less 'mature' than mDCs until activated.[60,61,64] Their ability to polarize CD4 responses towards Th1 or Th2 is variable and may be context-dependent.[65,66] In other systems pDC have been reported to induce regulatory T cells or tolerance, possibly related to their ability to sense DNA released from apopotic cells and notable expression of ILT7.[67,68] Failure of tolerance is linked to the autoimmune diseases systemic lupus erythematosus and psoriasis.[63]

CD14$^+$ dendritic cells

Many non-lymphoid tissues contain a modest population of CD14$^+$ HLA-DR$^+$ cells that express CD11c in common with monocytes but lack typical mDC markers such as CD1c or CD141, co-stimulatory molecules and CCR7.[3,29,56] These cells were originally identified as migrant CD14$^+$ populations from human skin.[27,28] They were previously referred to as 'interstitial-type' or 'dermal-type' DCs (to contrast with epidermal LCs) but this term is misleading because it ignores the major population of CD1c$^+$ interstitial mDCs.

CD14$^+$ DCs express DC-SIGN (CD209) and the macrophage markers FXIIIA and CD163, which may also be found on monocytes or monocyte-derived DCs and macrophages, especially those generated under tolerogenic conditions such as IL-10 or vitamin D.[3,69,70] *In situ*, it can be difficult to separate CD14$^+$ DCs from macrophages by antigen expression and recourse to the physical properties of side scatter, autofluorescence and ability to migrate from explanted skin, is required.[3] Somewhat confusingly, CD14$^+$ DCs acquire CD141 in culture but otherwise they do not resemble cross-presenting CD141$^+$ DCs, which are typically CD14 negative and cannot be made from monocytes.

CD14$^+$ DCs migrating from explanted human skin are less mature or more macrophage-like than CD1c$^+$ DCs and do not stimulate naive T cells efficiently.[8,29,71,72] CD14$^+$ DCs retain the ability to differentiate into LC-like cells or more mature DC-like cells *in vitro*.[42,71,73] Unstim-

ulated they have proven tolerogenic functions that can be recapitulated by treating monocytes with vitamin D.[44] Together these properties suggest that $CD14^+$ DCs may be extravasated, quiescent 'tissue monocytes'. Their turnover in bone marrow transplantation is rapid, and parallels blood myeloid engraftment, in contrast to long-lived macrophages.[3]

As $CD14^+$ DCs express little CCR7, their migration to lymph nodes is questionable[3,29] although discrete, possibly blood-derived $CD14^+$ $CD209^+$ cells are found in the paracortex.[22,32] Important functions have been ascribed to $CD14^+$ DCs in the formation of follicular helper T cells[56] or in providing direct B-cell help.[74]

The mouse equivalent of $CD14^+$ DCs is currently under scrutiny. As suspected from human biology, non-lymphoid tissue $CD11b^+$ DCs are heterogeneous and contain monocyte-derived cells with properties similar to $CD14^+$ DCs. New markers including CD24, CD26, CD64 and CX3CR1 are allowing a monocyte-derived component of the CD11b DC population to be identified.[75,76] Further confirmation of this would suggest by correlation, that $CD14^+$ human DCs are indeed monocyte-derived and shed new light on their *in vivo* function.

Langerhans cells

Langerhans cells reside in the supra-basal epidermis and other stratified squamous epithelia (bronchus, oral and genital mucous membrane) where they form a network. Human LCs express high levels of the C-type lectin Langerin and CD1a, a non-polymorphic class I MHC molecule. Both antigen capture and presentation molecules are found together in a specialized endosomal compartment, visible by EM as the Birbeck granule. Other markers include CD36, ATPase and FcεR1.[23,77]

Langerhans cells epitomize migratory tissue DC and have facilitated many studies of functional DC specialization across several species.[23] Their derivatives can easily be detected in skin-draining lymph nodes, especially in inflammatory skin disorders. They occupy the lymph node paracortex as $langerin^+$ $CD1a^{high}$ interdigitating cells.[78]

The function of LCs in immunity has been surprisingly difficult to pin down. They can be matured into potent cross-presenting DCs[39] but also lack critical TLRs and can induce regulatory T cells and IL-22 production through CD1a-restricted antigen to autologous T cells.[79] Overall, LCs appear to maintain epidermal health and tolerance to commensals, while retaining the ability to respond to selected intracellular pathogens and viruses under inflammatory conditions.

Inflammatory dendritic cells

It has been known for many years that highly functional DCs can be derived from classical $CD14^+$ blood monocytes, using GM-CSF and IL-4[80] or more subtle *in vitro* tissue models.[24] Monocyte-derived DCs have a wide range of properties including potent stimulation of naive $CD4^+$ T cells, cross-presentation to $CD8^+$ T cells and production of key cytokines IL-1, IL-6, TNF-α, IL-12 and IL-23.[53]

With correlative evidence that most primary DCs are probably not derived from monocytes, the challenge is to understand the role of inflammatory monocyte recruitment to human DC biogenesis *in vivo*. Monocytes are highly plastic and their differentiation into DCs or different forms of macrophages (M1/M2) *in vitro* provides a conceptual framework for inflammation. Human inflammatory exudates contain distinct inflammatory DC-like and macrophage-like cells and transcriptional profiling suggests a common monocyte origin.[9] Key features of these cells are the expression of CD1c, CD1a, CD206, FcεR1, SIRPα but lack of CD16 and CD209. *In vitro* they synthesize IL-1β, TNF-α, IL-6 and IL-23 and stimulate Th17 responses. Monocyte-derived DCs and inflammatory DCs in this study both express transcription factor zbtb46, in common with $CD1c^+$ DCs.[81,82] Previous descriptions of inflammatory DCs include inflammatory dendritic epidermal cells (IDECs), found in Th2-mediated atopic dermatitis, and TNF and inducible nitric oxide synthase-producing (TiP) DCs, found in psoriasis.[83,84] Together these data suggest that different inflammatory environments will generate monocyte-derived DC subsets with distinct functions. Many questions remain, including whether blood DCs also form inflammatory cells directly and whether inflammatory DCs migrate to lymph nodes or differentiate into steady-state resident cells after resolution of inflammation.

Non-classical monocytes and SLAN DCs

Human monocyte populations are heterogeneous[16] and $CD16^+$ monocytes possess distinct characteristics including higher MHC class II and co-stimulatory antigen expression that have led some authors to classify them as a type of blood DC.[20] In agreement with this view, a subset of $CD16^+$ monocytes characterized by expression of the antigen 6-Sulpho LacNAc (SLAN) is reported to secrete large amounts of TNF-α, IL-1β and IL-12 and to respond rapidly to inflammatory stimuli.[84] There is a lack of consensus, however. Gene expression analysis and functional studies suggest that $CD16^+$ $CD14^{dim}$ non-classical monocytes, including $SLAN^+$ cells, have low inflammatory activity and are homologous to murine Gr-1/Ly6C low 'patrolling' monocytes.[85] In this report, cytokine secretion and pro-inflammatory activity were attributed to intermediate $CD14^+$ $CD16^+$ monocytes. Anatomically, non-classical $CD16^+$ monocytes are well positioned to infiltrate tissues but it remains uncertain that they should be classified as DCs. Unsupervised

hierarchical clustering of gene expression data is unequivocal that all monocytes cluster independently of DCs.[5,8,10,11]

Origin of human dendritic cells

Human DCs arise from the bone marrow through a series of currently undefined precursors that may have both myeloid and lymphoid ancestry.[86] Bone marrow transplantation and human DC deficiency states indicate that continual replenishment from blood-borne precursors is required for tissue populations of $CD1c^+$, $CD141^+$ and $CD14^+$ DCs.[3,87,88] The potential role of blood DCs as precursors to tissue DCs has been outlined but there is a gap in knowledge between the bone marrow and peripheral blood compartments. Although Flt-3 and MHC class II expression has been useful for tracking restricted DC precursors in the mouse, they are less informative markers in humans because the entire $CD34^+$ progenitor compartment is positive.

Studies in humans with DC deficiency have begun to shed some light on the cellular pathways and genetic regulation of DC haematopoiesis.[88] By analogy with mice, it is likely that the early transcription factors Ikaros, PU.1, Gfi1 and Id2 are required for DC development in humans.[89,90] Ikaros and GFi1 defects have been characterized in humans but have much broader haematopoietic defects than suggested by murine models. Heterozygous *GATA-2* mutation induces a specific defect in mononuclear cell development, known as DC, monocyte, B and NK lymphoid (DCML) deficiency.[91]

Dendritic cell production from human progenitors is promoted by Flt-3 ligand, GM-CSF and IL-4 *in vitro*[35] and Flt-3, macrophage colony-stimulating factor (M-CSF) and GM-CSF signalling via signal transducers and activators of transcription 3 and 5 is likely to play an important role *in vivo*. Flt-3 is more highly expressed on DCs than monocytes or macrophages, in inverse relationship with M-CSF receptor.[8] Functional GM-CSF deficiency due to an autoimmune neutralizing antibody exists and causes defective function of alveolar macrophages but DC profiling has not been performed in detail.[92]

More specific defects in classical DCs have been reported in mice lacking interferon regulatory factor 4 (IRF4), IRF8 and Batf3 and in pDCs due to loss of E2-2.[89,90] In particular the balance between Id2 and E2-2 is critical in specifying myeloid or plasmacytoid DC development and E2-2-deficient humans have impaired pDC function.[57,93] Bi-allelic IRF8 deficiency in humans causes loss of all DCs and monocytes, in keeping with a broader pattern of human IRF8 expression than in mouse.[94] Batf3 knock-down by lentiviral short hairpin RNA inhibits the formation of $CD141^+$ DCs, a result that is more closely aligned to the selective loss of $CD8^+$ DCs in knockout mice.[45] The recently described transcription factor zbtb46 is specifically expressed in mDCs but is not required for the development of murine classical DCs.[81,82]

Human LCs have some self-renewal capacity independently of the bone marrow. Several reports have shown that they are proliferating cells[95,96] maintained in a hair follicle niche.[97] Human limb transplants show that they remain of donor origin, independent of the bone marrow,[98] although after haematopoietic stem cell transplantation, they are gradually replaced by bone-marrow-derived cells.[87] Humans lacking monocytes and all identifiable DC populations also maintain reasonable LC populations, ruling against monocytes or $CD14^+$ dermal DCs as steady-state precursors.[91] The ready derivation of LC-like cells from $CD34^+$ bone marrow progenitors or monocytes *in vitro*[99,100] is in keeping with observations in mice that blood-borne progenitors may be recruited to renew LCs after severe inflammation has destroyed their epidermal niches.[101] The development of LCs reflects a more macrophage-like ancestry than other DC populations. Treansforming growth factor-β is required for the acquisition of langerin in humans and M-CSF receptor rather than Flt-3 is critical for their development in mice.

Concluding remarks and future directions

Many years after the mononuclear phagocyte system was conceived and monocyte-derived DCs were discovered in humans, we perceive monocytes, macrophages and DCs more clearly but acknowledge ever more complexity in their origins and complementary functions. The specialized functions of human DC subsets and their derivation from DC-restricted precursors is beginning to be established and should lead to new therapeutic opportunities. However, much remains to be learned about DC haematopoiesis in humans in the steady state, and the pathological consequences of inflammatory generation of DCs from monocytes.

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Disclosures

The authors declare that they have no conflicts of interests.

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