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REVIEW

Human dendritic cell subsets and function in health and disease

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Abstract The method of choice for the development of new vaccines is to target distinct dendritic cell subsets with antigen in vivo and to harness their function in situ to enhance cell-mediated immunity or induce tolerance to specific antigens. The innate functions of dendritic cells themselves may also be targeted by inhibitors or activators that would target a specific function such as interferon production, potentially important in autoimmune disease and chronic viral infections. Importantly targeting dendritic cells requires detailed knowledge of both the surface phenotype and function of each dendritic cell subset, including how they may respond to different types of vaccine adjuvants, their ability to produce soluble mediators and to process and present antigens and induce priming of naïve T cells. This review summarizes our knowledge of the functional attributes of the human dendritic cell subsets in the steady state and upon activation and their roles in human disease.

Keywords Human dendritic cells · $CD141^+$ dendritic cells · $CD1c^+$ dendritic cells · Plasmacytoid dendritic cells · Cytokines · Innate immunity · Interferons · Antigen presentation

Abbreviations

Ag	Antigen
CTL	Cytotoxic T lymphocyte
DC	Dendritic cells
ESAM	Endothelial cell-selective adhesion molecule
Flt3	Fms-like tyrosine kinase 3
Flt3L	Fms-like tyrosine kinase 3 ligand
HCV	Hepatitis C virus
IFN	Interferon
IFN-I	Type I interferons
IFN-III	Type III interferons (also known as IFN-λ)
LC	Langerhans cells
MoDC	Monocytes-derived dendritic cells
Necl2	Nectin-like protein 2
NET	Neutrophil extracellular trap
PDC	Plasmacytoid dendritic cells
PAMPs or DAMPs	Pathogen or damage associated molecular patterns
PBMC	Peripheral blood mononuclear cells
Poly I:C	Polyinosinic:polycytidylic acid
PRR	Pattern recognition receptors
SLE	Systemic lupus erythematosus
SNP	Single nucleotide polymorphism
TGF	Transforming growth factor
TLR	Toll-like receptor
TSLP	Thymic stromal lymphopoietin
TNF	Tumor necrosis factor

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Introduction

Dendritic cells (DC) are sentinels of the immune system that initiate and direct immune responses. They are rare cells normally constituting 1 % or less of total haematopoietic cells of any lymphoid organ or blood. DC continually sample their environment, presenting antigen (Ag) to T cells and co-operatively directing tolerance or immunity, depending on their activation state. All DC are not the same and differ depending on the organ in which they are located, the danger signals they recognize and the type of soluble molecules they produce.

DC are activated by the sensing of danger in the form of pathogen or damage associated molecular patterns (PAMPs or DAMPS, respectively). Sensing of PAMPs and DAMPs is achieved through ligation of pattern recognition receptors (PRR) that are differentially expressed by DC subsets. Thus, the ability of a particular DC to respond to any given danger signal is dependent upon the PRR they express and their different and distinctive abilities to produce various cytokines and interferons (IFN). They endow DC with the ability to induce specific $CD4^+$ and $CD8^+$ T cell responses, including the $CD8^+$ cytotoxic T cell (CTL) and $CD4^+$ T helper (Th) 1 responses essential for driving immune responses against intracellular pathogens and cancer, $CD4^+$ Th2 responses required for immunity against parasitic infections, $CD4^+$ follicular helper T cells important for humoral responses and $CD4^+$ Th17 responses important for counteracting bacterial and fungal pathogens. DC also play an essential role in maintaining tissue homeostasis and immune tolerance, and dysregulation of such responses results in the pathogenesis of many diseases, including autoimmunity and allergy.

The phenotype and function of DC subsets in the mouse has been well characterized and recently reviewed [1]. The last 5 years has seen enormous progress in the phenotypic and functional characterization of human DC subsets [2, 3]. Here, we provide a comprehensive overview of human DC subsets and function, focussing on the key discrepancies between human DC and their murine counterparts, and their contribution to human disease pathology and immune regulation.

Human dendritic cells

Human DC can be found in most lymphoid and non-lymphoid tissues; however, studies on human DC have largely focused on blood as the most accessible source of tissue. They comprise approximately 1 % of circulating peripheral blood mononuclear cells (PBMC) and are classically defined as Ag-presenting leukocytes that lack other leukocyte lineage markers (CD3,14,15,15,19,20,56), express high levels of major histocompatibility complex (MHC) class II (HLA-DR) molecules ($lineage^-HLA\text{-}DR^+$) and have potent allo-stimulatory capacity [4, 5]. Like mouse DC, these can be broadly categorized into plasmacytoid (p)DC (defined as $CD11c^-CD123^+$ in humans) and conventional (c) DC (defined as $CD11c^+CD123^-$). Conventional DC in humans can be further divided into CD141 $(BDCA\text{-}3)^+$, $CD16^+$ DC and CD1c $(BDCA\text{-}1)^+$ DC subsets [6–9].

Human DC arise from $CD34^+$ haematopoietic precursors in the bone marrow that develop into monocyte-DC progenitors with the capacity to develop into monocytes, or the common DC progenitor [10]. The common DC progenitor gives rise to pDC and pre-cDC that migrate through blood and peripheral lymphoid tissues. The pre-cDC exclusively differentiate into $CD1c^+$ and $CD141^+$ DC subsets [11]. Other types of DC, collectively termed monocyte-derived DC (MoDC), differentiate separately from monocytes, particularly in response to inflammation.

As many of the markers used to define human DC are not expressed by mouse DC subsets and markers used to define DC in mice are not expressed by human DC (e.g., CD8), aligning mouse and human DC has been challenging for many years. Neither CD141 nor CD1c is exclusively expressed by the DC subsets they represent, further confounding definitive phenotypes and function. However, the identification of new subset-specific molecules, transcriptome and functional analyses have now identified the $CD141^+$ cDC subset as the human equivalent of the mouse $CD8^+/CD103^+$ cDC, and the $CD1c^+$ cDC subset as the equivalent of the mouse $CD11b^+$ DC [9, 12–14] (Table 1). Human pDC, $CD1c^+$ DC, $CD141^+$ DC and MoDC have unique gene expression profiles, predicting they each have specialized functions. However, the functional analyses on these subtypes are only just beginning and highlight similarities as well as key differences with their mouse counterparts.

The human $CD141^+$ DC subset

Human $CD141^+$ DC are found in blood, lymph nodes, spleen, tonsil, liver, lung, skin and intestine [8, 12, 15–18]. Detailed functional analysis of this subset, especially in peripheral tissues, has been limited due to their rarity (0.03 % of PBMC) and access to human tissue. Transcriptional analysis suggests high conservation of function between blood and tissue-derived $CD141^+$ DC and their mouse $CD8^+/CD103^+$ counterparts [9, 12, 14, 19]. $CD141^+$ DC express fms-like tyrosine kinase 3 (Flt3) and they can be differentiated by Flt3 ligand (Flt3L) from human CD34+ progenitors in vitro [18, 20] and in vivo [21], suggesting a dependence on Flt3L for development,

Table 1 Phenotype and function of human DC subsets

	$CD1c^+$ DC	$CD141^+$ DC	pDC	MoDC	LC	References
Mouse equivalent	$CD11b^+$ cDC	$CD8^+$ cDC	pDC	Inf DC	LC	[1, 64]
Location	Blood, lymphoid, non-lymphoid organs	Blood, lymphoid, non-lymphoid organs	Blood, lymphoid organs	Skin (steady state), inflamed tissues (inflammation)	Skin	[1, 162]
Phenotype	Lin^- $CD11c^+$ DR^+ Sirpα $(CD172a)^+$ $CD1c^+$ $CD14^{low}$ $CD11b^+$ $CD103^+$ (intestine only)	Lin^- $CD11c^+$ DR^+ $CD141^+$ XCR1$^+$ $CLEC9A^+$ $Necl2^+$	Lin^- $CD11c^-$ DR^+ $BDCA-2^+$ $BDCA-4^+$ $CD123^+$	Lin^- $CD11c^+$ DR^+ $CD1a^+$ $CD1c^+$ $CD14^+$ $CD11b^+$ FcεRI	Lin^- $CD11c^+$ DR^+ $CD1c^+$ Langerin$^+$ E-cadherin$^+$	[1, 162]
TLR expression	3 (low), 4 (low), 8	3, 8	7, 9	3 (low), 4, 7 (low), 8	3	[1, 30]
Cytokine profile	IL-12, IL-23, IL-10	Type III	Type I and III IFN	IL-1β, IL-6, IL-10, IL-23	ND	[12, 31, 33, 64, 73, 77, 78, 94, 100, 101, 150, 151]
Functions to date	Th2 induction in response to allergen, Th17 induction in response to fungal infection, immune regulation	Cross presentation of cellular Ag and immune complexes, CTL priming.	Type I IFN production against viral and fungal infections, immune regulation	Induction of Th1 and Th17 responses	Induction of Th2, CTL responses	[12, 16, 19, 31, 33, 42, 55, 85–87, 89, 100, 133–135, 144, 147–151, 162]

like their mouse counterparts. The requirement for transcription factors is less clear. Although they express Batf3 and require it for their development in vitro, $CD141^+$ DC can develop independently of Batf3 in vivo [16, 17]. They also express interferon regulatory factor 8 (IRF8) and were found to be dramatically reduced in patients with IRF8 mutations, suggesting a critical role for IRF8 in their development [22].

PRR expression and cytokine secretion by $CD141^+$ DC

$CD141^+$ DC express high levels of toll-like receptor (TLR) 3, which recognizes dsRNA [9, 23], and uniquely express the C-type lectin CLEC9A [24–26], nectin-like protein 2 (Necl2) [27] and chemokine receptor XCR1 [19, 28]. Unlike their mouse counterparts, $CD141^+$ DC do not produce high levels of IL-12 [12, 16, 18, 29]. Mouse $CD8^+$ DC are most effective at producing IL-12 following TLR4 or TLR9 ligation whereas human $CD141^+$ DC lack expression of these TLRs [29, 30], which may explain the discrepancy between these species. $CD141^+$ DC also express TLR8 but do not produce appreciable amounts of IL-12 or other cytokines in response to TLR8 ligation [29, 31] and produce only low or undetectable levels in response to a variety of stimulatory cocktails, including TLRs that synergistically enhance IL-12 production or secondary T cell-mediated signals [16, 18, 29, 31]. $CD11b^-$ cDC of human thymus (not co-stained with CD141 but presumed as the equivalent thymic subset) have been shown to produce IL-12 in response to CD40 ligation [32]. Thus, although there remains the possibility that $CD141^+$ DC may produce IL-12 in response to as yet unidentified factors, the considerable available evidence suggests they are not major producers of this cytokine.

New insights into the function of $CD141^+$ DC have been gained by the observation that these DC are major producers of type III IFN (IFN-III or IFN-λ) in response to TLR3 ligation, similar to their mouse $CD8^+$ DC counterparts [33]. The IFN-III family in humans consists of four members IFNL1 (IL-29), IFNL2 (IL-28A), IFNL3 (IL-28B) and IFNL4 which are structurally related to the IL-10 family but functionally related to type I IFNs (IFN-I) [34]. Several studies have demonstrated a critical role for IFN-III in protection against viruses that exhibit strong epithelial cell tropisms (e.g., rotavirus, norovirus), which cannot be compensated for by IFN-I [35, 36], and single nucleotide polymorphisms (SNPs) in the *IFN-lambda3* gene, leading to IFNL4 expression, have recently been linked with spontaneous and treatment-induced clearance of hepatitis C virus (HCV) infection [37, 38]. The precise function of IFNL4 and how this affects viral immunity is as yet unknown. Interestingly, $CD141^+$ DC numbers are

enriched in human liver [39, 40]. Although whether their numbers increase or decrease in liver disease is currently under debate [39–41], it is clear that lung and blood-derived CD141$^+$ DC are major producers of IFN-III in response to HCV or polyinosinic:polycytidylic acid (poly I:C) [33, 39, 40]. Thus, CD141$^+$ DC-derived IFN-III may play a crucial role in HCV infection and subsequent liver disease and cancer.

The role of CD141$^+$ DC in CD8$^+$ T cell responses

Human CD141$^+$ DC and mouse CD8$^+$ DC share features endowing them with the capacity to induce CD8$^+$ CTL responses that are essential for the eradication of tumors and many viruses including HCMV and HIV [16, 18, 19, 28]. Like their mouse CD8$^+$ DC counterparts, CD141$^+$ DC are efficient at cross-presentation, the process by which CD8$^+$ T cell responses are generated against tumors and pathogens that infect cells other than DC. CD141$^+$ DC particularly excel at cross-presentation of cellular Ag, immune complexes and Ag specifically targeted to late endosomes [12, 16, 19, 21, 28, 42, 43]. This is facilitated by their expression of CLEC9A, a receptor for dead cells, and TLR3, both of which are known to regulate cross-priming [44–48]. Cross-presentation of soluble protein by blood CD141$^+$ DC is enhanced after ligation with the TLR3 agonist, poly I:C [12, 16, 49], but the requirements of activation for cross-presentation by tissue CD141$^+$ DC is less clear. Skin CD141$^+$ DC can cross-present in the absence of activation and this can be enhanced with poly I:C alone or combined with additional stimuli [12]. In contrast, cross-presentation by splenic CD141$^+$ DC is not enhanced by poly I:C [49]. Lymph node CD141$^+$ DC also do not appear to require activation for cross-presentation but the effect of poly I:C was not examined in this study [50]. Optimal generation of CTL responses is also facilitated by exclusive expression of XCR1 by CD141$^+$ DC [19, 28]. The XCR1 ligand, XCL1, is secreted by activated CD8$^+$ T cells, acting as a powerful chemoattractant [51]. These features and their similarities to mouse CD8$^+$ DC point to a role for CD141$^+$ DC in the generation of anti-tumor and anti-viral CTL responses where cross-priming is considered crucial. Mouse CD8$^+$ DC are known to play a crucial role in anti-tumor immunity and accumulate in regressing tumors [52, 53]. Similarly, transcripts associated with CD141$^+$ DC in some human tumors positively correlate with patient outcome, providing the best correlative transcriptome signature with cancer patient survival to date [52]. This provides a strong rationale for specifically targeting the CD141$^+$ DC subset in particular for immunotherapeutic vaccines for cancer [30, 54].

The role of CD141$^+$ DC in CD4$^+$ T cell responses

CD141$^+$ DC are potent stimulators of allogeneic (donor MHC mis-matched) CD4$^+$ T cell proliferation in vitro, and are similar to CD1c$^+$ DC in this regard [14, 16, 29, 49, 55]. CD141$^+$ DC have the capacity to polarize CD4$^+$ T cells towards a Th1 phenotype, particularly after ligation of TLR3 [16, 29, 56, 57]. However, a number of these studies have reported that CD141$^+$ DC and CD1c$^+$ DC activated with a variety of stimuli are similarly effective in their ability to induce Th1 responses. Thus, unlike their mouse counterparts, there is not yet clear evidence to suggest that CD141$^+$ DC possess a specialized capacity to induce Th1 responses. This is perhaps not unexpected given the importance of IL-12 in Th1 induction and the findings that CD141$^+$ DC are not major producers of this cytokine. CD141$^+$ DC are superior to CD1c$^+$ DC at inducing Th2 responses after stimulation with live-attenuated influenza virus [55], an observation that would not have been predicted from mouse studies, where the CD11b$^+$ DC are more efficient in promoting Th2 responses. Differences in Th differentiation between human and mouse systems may be explained by the models and assays used. In humans, stimulation of allogeneic CD4$^+$ T cells in vitro is the standard means of assessing CD4$^+$ T cell priming and polarization by human DC, but may not accurately reflect the role of DC in autologous Ag-specific CD4$^+$ T cell priming induced by pathogens and other insults. In the few studies where responses to autologous memory CD4$^+$ T cells have been examined, CD141$^+$ DC and CD1c$^+$ DC were similar in their capacity process and present Ag to autologous memory CD4$^+$ T cells [16, 42] and to promote Th1 responses following activation with *Aspergillus fumigatus* [56].

A number of studies have pointed to a role for mouse CD8$^+$ DC in the induction of central and peripheral tolerance [1] but a similar role for human CD141$^+$ DC is yet to be described. Although skin CD141$^+$ DC were originally reported to exert tolerogenic function [58], these DC were also CD14$^+$ and subsequently identified as being cells of monocyte origin rather than bonafide CD141$^+$ DC [59]. This reinforces the need for careful phenotyping of classical CD141$^+$ DC, particularly given the promiscuous expression of the CD141 molecule.

The human CD1c$^+$ DC subset

Human CD1c$^+$ DC can be found in lymphoid and non-lymphoid tissues, including blood, lymph nodes, tonsils, spleen, skin, liver, kidneys, lungs and gut [12, 14, 49, 57, 60–65]. Transcriptome analysis demonstrates a clear relationship between CD1c$^+$ DC in these different tissues

with mouse CD11b$^+$ DC and therefore suggests a high likelihood of conserved function [12–14]. However, there are also considerable tissue-specific discrepancies, indicating that CD1c$^+$ DC are more readily influenced by local environmental cues and may have different specialized functions in various organs [14]. Examples of these are CD1a expression by dermal CD1c$^+$ DC and CD103 expression by intestinal CD1c$^+$ DC. CD1c$^+$ DC in human blood are characterized by expression of CD11c, CD11b, CD1c, MHC-II, CD45RO and SIRPα (CD172a) [6, 7, 49]. Unlike their mouse counterparts, human CD1c$^+$ DC do not express endothelial cell-selective adhesion molecule (ESAM). The marker CD1c does not exclusively identify this DC subset as it is also expressed on a subpopulation of B cells and can be induced on other cell types, including MoDC and CD141$^+$ DC [6, 18, 21]. CD1c$^+$ DC are often difficult to discern from human MoDC due to similar expression patterns of MHC-II, CD11c, CD11b and CD1c [64]. Thus, some functions assigned to CD1c$^+$ DC, particularly in inflamed tissues, may need re-evaluation with new markers such as expression of Flt3 and IRF4 [56, 61, 63], and the absence of the monocytic marker, CD64 (FcγR1) [66–68], that now allows more precise segregation of bonafide CD1c$^+$ cDC from MoDC. Transforming growth factor (TGF)-beta induces the expression of Langerin on CD1c$^+$ DC in human tissues and all DC expressing Langerin in human tissues are CD1c$^+$. This is an important distinction with the mouse DC network, where Langerin expression is restricted to the CD8$^+$/CD103$^+$ DC and Langerhans cells [69].

Like their mouse counterparts, CD1c$^+$ DC numbers expand in response to Flt3L [11, 21, 70–72]. Their high IRF4 expression is consistent with a requirement for this transcription factor for development of their mouse counterparts. Human subjects with IRF8 mutations are deficient in CD1c$^+$ DC, providing evidence that this transcription factor is essential for their development [22]. Although the K108E IRF8 mutation results in the loss of all DC subsets and a dramatic reduction in monocytes, the T80A IRF8 mutation is selectively deficient in CD1c$^+$ DC. Both mutations result in increased susceptibility to mycobacterial infection, implying a role for CD1c$^+$ DC in anti-mycobacterial immunity. Further supporting this, CD1c$^+$ DC, but not CD141$^+$ DC or pDC, engulf *Mycobacterium tuberculosis* (*Mtb*) and produce IL-6 and tumor necrosis factor (TNF) [73]. The CD1c molecule itself is a human-specific non-classical MHC that presents mycobacterial glycolipid Ag to T cells [74]. CD1c-restricted Ag-specific T cells are found in patients with *Mtb* infection but not healthy controls, but the role of CD1c$^+$ DC in inducing these responses is yet to be examined [74].

PRR expression and cytokine production by CD1c$^+$ DC

Unlike CD141$^+$ DC, receptors specifically expressed by CD1c$^+$ DC which might provide further insights into their function are yet to be identified. CD1c$^+$ DC express most TLR at low levels, with the exception of TLR7 and TLR9 [29]. In contrast to their mouse counterparts, accumulating evidence suggests that CD1c$^+$ DC are major producers of IL-12, particularly in response to stimulation via TLR8, an endosomal receptor that recognizes bacterial and viral ssRNA. Although CD1c$^+$ DC and CD141$^+$ DC express similar levels of TLR8 mRNA and upregulate costimulatory molecules after stimulation with TLR8 ligands [29, 75], only CD1c$^+$ DC produce IL-12p70, IL-1β, TNF and IL-6 in response to TLR8 ligation [22, 29, 75–78]. CD1c$^+$ DC also produce IL-12 after stimulation with mycobacteria and IFN-γ [77] but not after mycobacterial stimulation alone [73], which highlights their dependency on additional stimuli for optimal IL-12 production. Stimulation with a broad range of other PRRs have failed to induce significant amounts of IL-12 by CD1c$^+$ DC [16, 29, 31, 75]. However, TRIF-coupled TLRs such as TLR3 or TLR4 act in synergy with TLR8 to dramatically enhance IL-12 production by CD1c$^+$ DC [31, 78]. This contrasts with their mouse CD11b$^+$ counterparts, which are not known to produce high IL-12 and suggests a role for CD1c$^+$ DC in the generation of Th1 responses.

Concomitant with IL-12 production following TLR8 ligation or mycobacterial stimulation of CD1c$^+$ DC is secretion of IL-23 [76–78] and lung CD1c$^+$ DC constitutively express IL-23p19 [56]. Furthermore, specific production of IL-23 but not IL-12p70 upon TLR4 and TLR7/8 stimulation was observed in intestinal CD1c$^+$ DC [76]. This suggests that CD1c$^+$ DC may also have the capacity to induce Th17 immune responses that are important in responses against a range of bacterial and fungal pathogens, similar to their equivalent mouse CD11b$^+$ DC subset.

TLR8 ligation and production of IL-12 and IL-23 by CD1c$^+$ DC could play a role in autoimmunity where pathogenesis is driven by self-RNA autoantibody complexes, which are also recognized by TLR8 [79, 80]. Despite mouse TLR8 being poorly characterized and unresponsive to human TLR8 ligands, there is emerging evidence in both species to support a key role for TLR8 in autoimmune pathogenesis [81–83], although a precise role for CD1c$^+$ DC is yet to be established.

The role of CD1c$^+$ DC in CD4$^+$ T cell responses

Accumulating evidence suggests that mouse CD11b$^+$ DC are specialized in the induction of CD4$^+$ T cell responses

and in particular, Th2 and Th17 responses. Various studies have shown that CD1c$^+$ DC can induce Th1, Th2 and Th17 responses, suggesting remarkable functional plasticity and potentially important roles in a variety of human conditions. CD1c$^+$ DC express higher levels of genes associated with MHC Class II processing such as Ifi30, HLA-DMA, cathepsin H and cathepsin S [16], supporting a role for this subset in CD4$^+$ T cell responses. As mentioned, the few studies performed to date suggest a similar capacity for CD1c$^+$ DC and CD141$^+$ DC to process and present Ag to CD4$^+$ T cells, induce CD4$^+$ T cell proliferation and polarize Th1 responses [16, 29, 55]. However, in these studies, CD1c$^+$ DC were not stimulated under conditions in which they optimally produce IL-12, where superior Th1 responses might be expected. Both subsets harbor the capacity to induce production of the Th2 cytokines, IL-4 and IL-13, by allogeneic CD4$^+$ T cells [16, 29, 55, 57], and in the intestine both subsets can polarize CD4$^+$ T cells to produce the Th17 cytokine, IL-17 [14]. Thus, the capacity of human DC to polarize CD4$^+$ T cell responses does not appear to be restricted to a particular subset and is likely to be influenced by the environmental stimuli. There are a few studies pointing to a role for CD1c$^+$ DC in CD4$^+$ T cell responses using autologous T cell models. CD1c$^+$ DC infected with mycobacteria induce Th1, Th17 and regulatory T cell signatures in autologous naïve CD4$^+$ T cells [73]. Whilst lung CD1c$^+$ DC and CD141$^+$ DC activated with *Aspergillus fumigatus* induce similar levels of IFNγ by autologous CD4$^+$ T cells, CD1c$^+$ DC are superior at inducing IL-17 production [56]. This is consistent with their ability to produce IL-23 and also with the role of their mouse CD11b$^+$ counterparts in the induction of Th17 immunity to counteract bacterial and fungal pathogens [56, 63, 76, 78].

Mouse CD11b$^+$ DC are major drivers of Th2 responses in allergy and asthma and emerging evidence suggests that CD1c$^+$ DC may be involved in this process [67]. CD1c$^+$ DC numbers are significantly increased in circulation of allergic rhinitis patients [84] and after allergen challenge in asthmatic patients [85], supporting a role for these DC in driving allergic pathology. The epithelial cytokine, thymic stromal lymphopoietin (TSLP), is upregulated in the airway mucosa of allergic rhinitis patients and promotes allergic inflammation correlating with the induction of Th2 responses [86, 87]. CD1c$^+$ DC in human airway mucosa are the main DC subset constitutively expressing the TSLP receptor (TSLPR) [85], and this is upregulated on CD1c$^+$ DC in the blood and airway mucosa of allergic asthmatic patients [88]. Furthermore, blood CD1c$^+$ DC from allergic patients pulsed with TSLP, house dust mite or grass pollen allergens induce autologous allergen specific T cell proliferation and Th2 cytokine production [85, 89]. PDC are limited in their capacity to induce autologous allergic Th2 responses [85, 89] and although CD141$^+$ DC were not examined, the lack of significant numbers of CD141$^+$ DC in the mucosa of allergic patients before or after allergen challenge and their weak expression of TSLPR argues against a major role for this subset [85]. Mouse models have shown that both CD11b$^+$ DC and MoDC contribute to the allergic response [67]. Although exclusion of CD14$^+$ cells was used to distinguish bonafide CD1c$^+$ DC from cells of monocyte origin in one of the human studies [85], revisiting CD1c$^+$ DC phenotype in allergic patients with the inclusion of more definitive markers such as Flt3, CD64, and IRF4 will be required to more precisely delineate the contributions of CD1c$^+$ DC and MoDC in human allergic tissue.

Induction of CD8$^+$ T cell responses by CD1c$^+$ DC

There is considerable evidence to demonstrate that CD1c$^+$ DC have the capacity to induce CD8$^+$ T cell responses. Depending on the nature of Ag, the DC location and activator, numerous studies have shown CD1c$^+$ DC to be equivalent to CD141$^+$ DC in their capacity to stimulate Ag-specific CD8$^+$ T cells [16, 31, 42, 49, 57]. Examples of this include direct Ag presentation by peptide loading or viral infection and cross presentation of long peptides, soluble protein or Ag targeted to early endosomes. These observations are not dissimilar to the mouse where there are numerous examples demonstrating that CD11b$^+$ DC are efficient at direct- and cross-presentation of certain types of Ag [90]. Blood CD1c$^+$ DC stimulated with combinatorial TLR4/8 agonists are especially potent at stimulating CD8$^+$ T cells in an IL-12 dependent manner [31]. Lung CD1c$^+$ DC are specialized in their ability to instruct naïve and memory CD8$^+$ T cells to acquire CD103, facilitating their migration and retention in peripheral tissues [91]. Thus, the generation of CD8$^+$ T cell responses does not appear to be restricted to any particular human DC subtype, and more thoroughly defining the roles of different DC subsets in different aspects of CD8$^+$ T cell immunity is an important area for future investigation.

The role of CD1c$^+$ DC in immune regulation

A number of studies point to a role for CD1c$^+$ DC in regulation of immune responses and maintaining tissue homeostasis, similar to their mouse CD11b$^+$ counterparts. Intestinal CD1c$^+$ DC express CLEC4A (DCIR) [14], a negative regulator of DC expansion that plays a crucial role in maintaining homeostasis and prevention of autoimmunity [92]. CD101, an immune regulatory molecule whose dysregulation is associated with autoimmune disease in humans [93], is also expressed by intestinal CD1c$^+$ DC [14]. Other genes involved in immune regulation expressed

by $CD1c^+$ DC include inhibitory receptors PILRA and TGFBR2; IRAK3, a negative regulator of TLR signaling; and VSIG4, a negative regulator of T cell activation [14]. $CD1c^+$ DC also express genes involved in regulating IL-22 signaling, suggesting a role in the regulation of the pathological responses promoted by this cytokine in the intestine [14]. These genes implicate $CD1c^+$ DC in the regulation of a diverse array of immune regulatory responses.

A role for $CD1c^+$ DC in immune regulation is further supported by studies demonstrating that $CD1c^+$ DC secrete IL-10 concomitantly with little or no pro-inflammatory cytokines in response *E. coli* or LPS and are effective at inducing T cells with immunosuppressive function [15, 94]. This feature is more prominent in $CD1c^+$ liver DC, suggesting they may be particularly important for maintaining tolerance in this organ [15]. Intestinal $CD1c^+$ DC are also effective inducers of regulatory T cells [14]. Intestinal epithelial cells produce factors such as TSLP and TGF that drive regulatory T cell induction by $CD1c^+$ DC [95]. All-*trans*-retinoic acid (RA) production is catalyzed by retinal dehydrogenase (RALDH2) and plays a critical role in maintaining intestinal immune homeostasis in mice by promoting the induction of gut-homing regulatory T cells. $CD1c^+$ DC express high levels of RALDH2, particularly in response to known immunosuppressive factors such as, 1α,25-dihydroxyvitamin D3 (Vitamin D_3) and this is exacerbated by RA, which is also expressed by intestinal epithelial cells [96]. RALDH2 expressing $CD1c^+$ DC induce naïve $CD4^+$ T cells to produce high IL-4, IL-5, IL-13 and IL-10 in vitro, although suppressive capacity of these cells could not be confirmed [96]. High expression of regulatory molecules ILT4, ICOS-L and PD-L1, production of IL-10 and differentiation of IL-10 secreting suppressive T cells by $CD1c^+$ DC may be a driving force behind the immune suppression observed in patients with chronic obstructive pulmonary disease (COPD) [97]. Collectively these observations suggest that environmental cues in non-lymphoid tissue likely precondition $CD1c^+$ DC towards an immune-regulatory phenotype in the steady state. Thus, $CD1c^+$ DC may be crucial for maintaining immune homeostasis and dysregulated function would, therefore, drive autoimmune responses or contribute to immunosuppressive conditions.

Human pDC

In the steady state pDC are found in blood and lymphoid organs and are rare in healthy nonlymphoid tissue [98]. Their transcriptomes, phenotype and function are largely conserved between mouse and humans. The pDC were originally defined by function- as the 'natural IFN-producing cells' of human blood [98]. Indeed human pDC have an amazing ability to produce type-I IFN (IFN-I) in response to TLR7 or 9 ligation [99]. The pDC also produce large amounts of IFN-III important in mucosal anti-viral responses [40, 100]. The production of IFNs in response to TLR7 and 9 ligation is tightly conserved between mouse and human pDC. Given their major production of IFNs the pDC are considered important in anti-viral immunity but their role in immune responses extends beyond responses to viruses.

Unlike mouse pDC, human pDC lack expression of CD11c and can be defined as Lineage negative, $CD11c^{-}$ $CD123^+HLADR^+BDCA2^+BDCA4^+CD45RA^+$ cells [98, 101]. Also unlike the mouse pDC, human pDC have an improved ability to stimulate naïve T cells although they are generally not as proficient as cDC [102].

CD2 can be utilized to further define two subsets of human pDC, both in blood and in tonsils [103, 104]. Both $CD2^{hi}$ and $CD2^{lo}$ subsets produce large amounts of IFN-I in response to viral stimulation. Both subsets are also capable of producing multiple pro-inflammatory cytokines including MIP-1a and IP-10 but only the $CD2^{hi}$ pDC produced IL-12p40 in response to influenza infection. Moreover, $CD2^{hi}$ pDC are more efficient at stimulating naïve $CD4^+$ and $CD8^+$ T cells than the $CD2^-$ cells [104]. Both subsets of pDC express Granzyme B but $CD2^+$ cells additionally express lysozyme, suggesting that they may be superior in lytic activity than their $CD2^{lo}$ counterparts [104]. The data generated to date do not support that CD2 defines different differentiation states of pDC but rather distinct functional subsets.

A human pDC subset expressing $CD56^+$ has recently been characterized. These $CD56^+$-pDC-like cells also express CD2, CD46, CD13 and CD33. Present at much lower numbers than pDC in peripheral blood, the authors propose these cells are an immature form of pDC [105]. Others propose these cells are potentially more closely related to cDC [106], whilst another group has reported that CD56 expression can be upregulated on pDC activated with FSME, a preventive vaccine for tick-borne encephalitis virus infections [107]. These activated $CD56^+$ pDC displayed enhanced T cell stimulatory and tumoricidal activity. Given the similarity in phenotype to an aggressive cancer, blastic plasmacytoid dendritic cell neoplasm (reviewed in [108] and [109]), thought to derive from pDC, it is important to determine exactly what the $CD56^+$ pDC-like cells correspond to, whether these are a differentiation state of pDC or cDC or whether they may correspond to a distinct cell type. It is of note that a pDC-like cell with the ability to display pDC and cDC functions has been described in mice that appears to correspond to a pDC-like cell that acquires cDC attributes upon inflammatory stimulus, including GM-CSF [110, 111], an

attribute shared by the cells described by Osaki et al. [105]. Further clonal studies in mouse will be required to further define the precursor nature of these cells.

pDC and immunity to pathogens

The production of large amounts of IFN has solidly placed the pDC as important players in anti-viral responses. Indeed human pDC have been shown to respond to numerous human pathogenic viruses with high level IFN production. In particular, the pDC response to HIV has been widely studied [112]. Human pDC are excellent conduits for the virus due to the expression of the HIV receptors CD4, CCR5 and CXCR4 on this DC subset [113] or highly responsive to it with IFN-I production in vitro [114]. Furthermore, HIV-infected pDC are poor presenters of viral Ag to T cells [115], resulting in the induction of regulatory T cells via production of IDO [116].

Human pDC also produce high levels of IFNs in response to non-viral pathogens. The human fungal pathogen *Aspergillus fumigatus* induces IFN-I production by pDC in a Dectin-2 dependent manner [117]. The responses of pDC to BCG, in particular granzyme B secretion, and cross-talk with human cDC are thought to be important for optimal $CD8^+$ T cell responses to BCG vaccine [102]. Moreover, priming and expansion of $CD4^+$ T cells by $CD1c^+$ cDC in Mycobacterium patients is enhanced by the presence of granzyme-B producing pDC [73]. Michea et al. [119] have elegantly shown that both blood and tonsillar pDC are activated by various gram positive and negative bacteria, resulting in production of IFNα and inflammatory cytokines and to priming of $CD4^+$ naïve T cells. Interestingly this study showed that soluble products produced by epithelial cells could greatly reduce the cytokine and IFN response of the pDC in response to bacteria, without affecting their upregulation of co-stimulation markers and their ability to prime naïve T cells. The authors suggested that epithelial cells at mucosal surfaces may restrict the pDC local inflammatory response to bacteria but support their ability to induce an adaptive immune response [119]. The ability of activated pDC to upregulate CCR6 or CCR10 and migrate to mucosal and/or skin epithelia [120] certainly gives them the tools to tackle bacterial infections and is relevant for their role in autoimmune disease.

The response of pDC to non-pathogenic bacteria is also potentially relevant to diseases that are affected by the microbiota. Yogurt fermented with *Lactococcus lactis* JCM5805 was able to activate human pDC in vivo [118], supporting a potential role of pDC in the immunity enhancing activity of probiotics.

pDC and autoimmune and inflammatory disease

In correlation with GWAS identifying IFN-I production or response genes, many SLE patients carry an 'IFN signature' [121], that is, evidence in PBMC of the expression of IFN-stimulated genes (ISGs) that are dependent on IFN-I (IFN-α and IFN-β) for transcription. Given the multifactorial nature of SLE, the involvement of different organ systems in different patients, and the relapsing/remitting nature of the disease, it is perhaps not surprising that not all patients would always carry an IFN signature, or indeed any ubiquitous biomarker. In 1979, researchers showed for the first time that IFN was present in the serum of SLE patients [122]. In SLE patients, the IFN signature is thought to be predominantly produced by IFN-I production by pDC in response to nucleic acid/autoantibody complexes via TLR7 and TLR9 [121, 123, 124], as has been shown in vitro. Delivery of nucleic acid complexes to pDC is dependent on FcR that bind anti-nucleic acid immune complexes [123] or via neutrophil extracellular traps (NETs). IFN-I production in SLE, or at least the induction of ISGs, is a major contributor to the etiology of disease since it enhances activation of DC, self-reactive B cells and T cells and the production of many other inflammatory cytokines.

The skin of psoriasis patients carries an IFN signature, implicating pDC in pathogenesis of this disease. Anti-microbial peptides including LL37, human beta defensin and lysozyme produced by keratinocytes of psoriatic patients all act as carriers to deliver self nucleic acids to endosomal compartments of pDC to induce high IFN-α levels in the skin [125].

Wiskott-Aldrich syndrome (WAS) is an X-linked primary immunodeficiency due to mutations in the WAS protein (Wasp) and characterized by recurrent infections. Patients have a clear predisposition to develop autoimmune conditions. Recently, it has been shown that WASP patients have elevated IFN-I in the serum and a clear IFN signature in PBMC [126]. Purified pDC from WAS patients show a constitutive IFN production and an elevated production of IFN-I upon CpG stimulation, pointing to a role of Wasp in the normal control of IFN production by pDC and a role of dysregulated pDC IFN-I production in the propensity of WAS patients to develop autoimmune disease [126].

LL37 and pDC are increased in artherosclerotic lesions, raising the possibility of pDC-derived IFN-I driving or at least contributing to these inflammatory lesions and to the increase in anti-dsDNA antibodies observed in advanced artherosclerotic patients [127].

Confounding the role of pDC in autoimmune diseases, often more prevalent in females, is the finding that X-chromosome dosage (TLR 7 is encoded on the X

chromosome) and estrogens, both contribute to enhanced IFN-I production by pDC from females [128].

pDC and tolerance

Although the pDC have a remarkable pro-inflammatory function via their IFN-I production, they have also been associated with protection from allergy [129] and a role in oral [130, 131] and transplant tolerance (reviewed in [132]). Mechanisms of tolerance induction and/or immunosuppression by non-activated pDC probably include, but are not limited to, their ability to produce IDO [133] and to induce regulatory T cells [134, 135]. In mice transgenic for the human pDC-specific BDCA2 Ag, pDC targeting via BDCA2 leads to regulatory T cell induction and tolerance [136]. In a number of clinical transplant settings, an increase in the pDC:cDC ratio correlates with improved graft survival (reviewed in [132]). In line with these observations pointing to a tolerogenic role for pDC, an increase in pDC number is often associated with a poor outcome in solid tumor patients [137]. What is clear is that we need to further understand whether pDC associated with tolerance are always non-activated or whether radiation-induced danger signals activate pDC in situ, actively directing tolerogenic function or whether tumor microenvironments actively suppress pDC pro-inflammatory function. These facts are essential if we are to harness pDC targeting strategies for anti-tumor therapies [137].

Human monocyte-derived DC

In vitro-derived MoDC

The majority of knowledge gathered over the past two decades on human DC function has been obtained from DC derived from monocytes differentiated in vitro by culture with GM-CSF and IL-4 [138]. The addition or substitution of cytokines, growth factors and other stimuli to the culture provides a versatile system for skewing DC with potent CTL,Th1,2,17 or regulatory functions and these studies have provided important insights into the functional plasticity of human DC and the initiation and regulation of human immune responses. They have also been extensively used in the clinic, mostly as vaccines to induce anti-tumor immune responses in cancer patients [30]. Despite some overlap in phenotype and function, especially with $CD1c^+$ DC, this DC phenotype is genetically distinct from $CD1c^+$ DC and $CD141^+$ DC and arises from a different bone marrow precursor population [10, 12, 13]. Although the physiological relevance of MoDC is unclear, the alignment of these cells with DC found in human inflamed tissues suggests them to be most closely related to inflammatory DC [64].

MoDC in the steady state

Human dermis contains an additional population of DC, usually referred to as $CD14^+$ dermal DC, that are distinct from $CD141^+$ DC and $CD1c^+$ DC (sometimes also referred to as skin $CD1a^+$ DC) [61, 139, 140]. $CD14^+$ dermal DC are poor stimulators of allogeneic T cells and instead secrete IL-10 and IL-6 and induce regulatory T cells [12, 58, 141–143]. They also play a specialized role in the development of humoral B cell responses by promoting the differentiation of $CD4^+$ T cells into follicular Th cells that prime naïve B cells to become plasma cells [144]. However, recent transcriptome analysis has revealed that these cells more closely resemble tissue resident macrophages than DC and are most likely to be derived from monocytes [145]. Another DC subset with a genetically distinct signature from resident $CD141^+$ DC and $CD1c^+$ DC subset has been identified in human intestine as $lineage^-MHC\ classII^+CD11c^+CD103^-Sirp\alpha^+$ [14]. Whilst the transcriptome of this subset more closely aligns with monocytes, it is considered more "DC" than "macrophage-like" on the basis of expression of CD11c, lack of CD14 and CD64 and potent stimulatory capacity of allogeneic T cells. Compared with resident $CD141^+$ DC and $CD1c^+$ DC, this DC subset was more effective at inducing IFN-γ by $CD4^+$ T cells, suggesting a role in Th1 responses. These studies highlight the complexity and often overlapping functions of the DC and monocyte/macrophage networks.

Inflammatory DC

Myeloid DC infiltrate the inflamed tissues of many human autoimmune diseases including the epidermis and dermis of psoriatic lesions, synovial fluids of rheumatoid arthritis patients, and inflamed intestinal tissue in Crohn's disease patients [64, 146–151]. They can also be found in the ascitic fluid of patients with breast and ovarian cancers [64]. These DC are characterized by an activated phenotype, high production of proinflammatory cytokines in including IL-12, IL-23, and an ability to induce both IL-17 and IFN-γ production by $CD4^+$ T cells. This dual Th1 and Th17 phenotype drives autoimmune pathology, suggesting a key role for infiltrating DC in the pathogenesis of these diseases [64, 152, 153]. DC derived from human inflammatory tissues express CD1a, CD1c, FcεR1, CD206, CD14, CD11b, M-CSFR and ZBTB46 [64]. Although previously described as "$CD1c^+$ DC" in rheumatoid arthritis synovial fluid [147–149], transcriptome analyses showed these cells to be most closely related to in vitro-derived MoDC and of monocyte origin, and therefore the likely human equivalents of the mouse "inflammatory" DC [64]. These data provide evidence to suggest that

inflammatory DC may be the main drivers of many autoimmune pathologies and may also contribute to tumor pathogenesis.

Langerhans cells

Langerhans cells (LCs) are the main Ag-presenting cells in the epidermis of human skin and have been considered as the classical sentinels that are the forefront of contact with invading microbial pathogens. Human Langerhans cells are self-renewing in the steady state but can also be repopulated from bone marrow precursors after inflammation or bone marrow transplantation [154]. Although LC can be derived from monocytes in vitro, they can also differentiate from $CD1c^+$ DC [155]. LC are characterized by expression of langerin (CD207) that functions as a receptor for microbial pathogens, and E-cadherin, which facilitates adhesion with nearby keratinocytes [156]. Human LCs are powerful stimulators of $CD4^+$ T cell proliferation and induce polarization towards a Th2 phenotype [144]. Human LCs can cross-present [157, 158] and are potent stimulators of naïve $CD8^+$ T cells [144], although studies in mice do not support this [32, 159] . Although LC have been implicated in the inhibition of inflammation and the induction of tolerance in mice, these functions are yet to be addressed in humans.

Concluding remarks

Human DC can now be divided into four major genetically distinct subclasses defined as $CD141^+$ DC, $CD1c^+$ DC, pDC, MoDC. These can be largely aligned with equivalent subsets in the mouse, defined as $CD8/CD103^+$ DC, $CD11b^+$ DC, pDC and MoDC, respectively. However, there are some key differences, particularly in PRR expression and cytokine production that require careful consideration when translating DC biology across species. Functional specializations of the human DC subsets are becoming increasingly apparent. Human pDC have long been known as the major IFN-I producers, playing a critical role in anti-viral immunity. The $CD141^+$ DC subset is a major producer of type III IFN specifically in response to TLR3 ligation, implicating them as important mediators against viruses such as HCV. Their phenotypic and functional characteristics along with the presence of associated transcripts in human tumors identifies this subset as a key subset to target vaccines aimed at generating CTL responses against tumors and many pathogens for which there are currently no effective vaccines. $CD1c^+$ DC are the main producers of IL-12, a key discrepancy between mouse and human systems. These DC are now implicated in the generation of immune responses to mycobacterial and fungal infections and in Th2-mediated allergic responses. Both $CD1c^+$ DC and pDC are emerging as key regulators of immune homeostasis and their dysregulation is implicated in the development of autoimmune diseases.

Despite their unique functions, human DC subsets also display a remarkable degree of plasticity and overlapping function. Although it is clear that all human DC are capable of generating $CD4^+$ and $CD8^+$ T cell responses, further subset specialization will likely be revealed temporally in the context of specific pathogens and other insults. This is particularly relevant to MoDC, which display considerable overlap in phenotype and function with $CD1c^+$ DC. $CD1c^+$ DC are present in tissues in the steady state where maintenance of homeostasis and initial priming of immune responses is important. In contrast, MoDC are rapidly differentiated from monocytes and infiltrate tissues in response to inflammation. Their role is therefore likely to be more specialized in driving local responses such as the activation of tissue resident effector memory T cells [160] to expedite and exacerbate immune responses and immunopathology. The interaction and cross-talk between different DC subsets will also likely be important in augmenting immune responses and is presently uncharted territory. Comprehensive direct functional comparisons of human DC subsets in response to different stimuli may also reveal further subset specializations. Such studies have been limited and are difficult to perform on rare human cells in vitro. The development of new models to investigate human DC function, such as humanized mouse models, in which functional human DC subsets develop in vivo [18, 21, 55, 75], and new culture systems to generate human DC subsets from $CD34^+$ progenitors in vitro [11, 18, 161], will greatly facilitate studies to enhance our understanding of human DC biology.

New insights into these remarkable cells and their role in human diseases will likely reveal a plethora of new immunotherapeutic interventions targeting specific DC subsets or their products, for treatment of a variety of human conditions including pathogen infections, cancers, autoimmune diseases and allergy.

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