Human dendritic cell subsets: An updated view of their ontogeny and functional specialization

Elodie Segura

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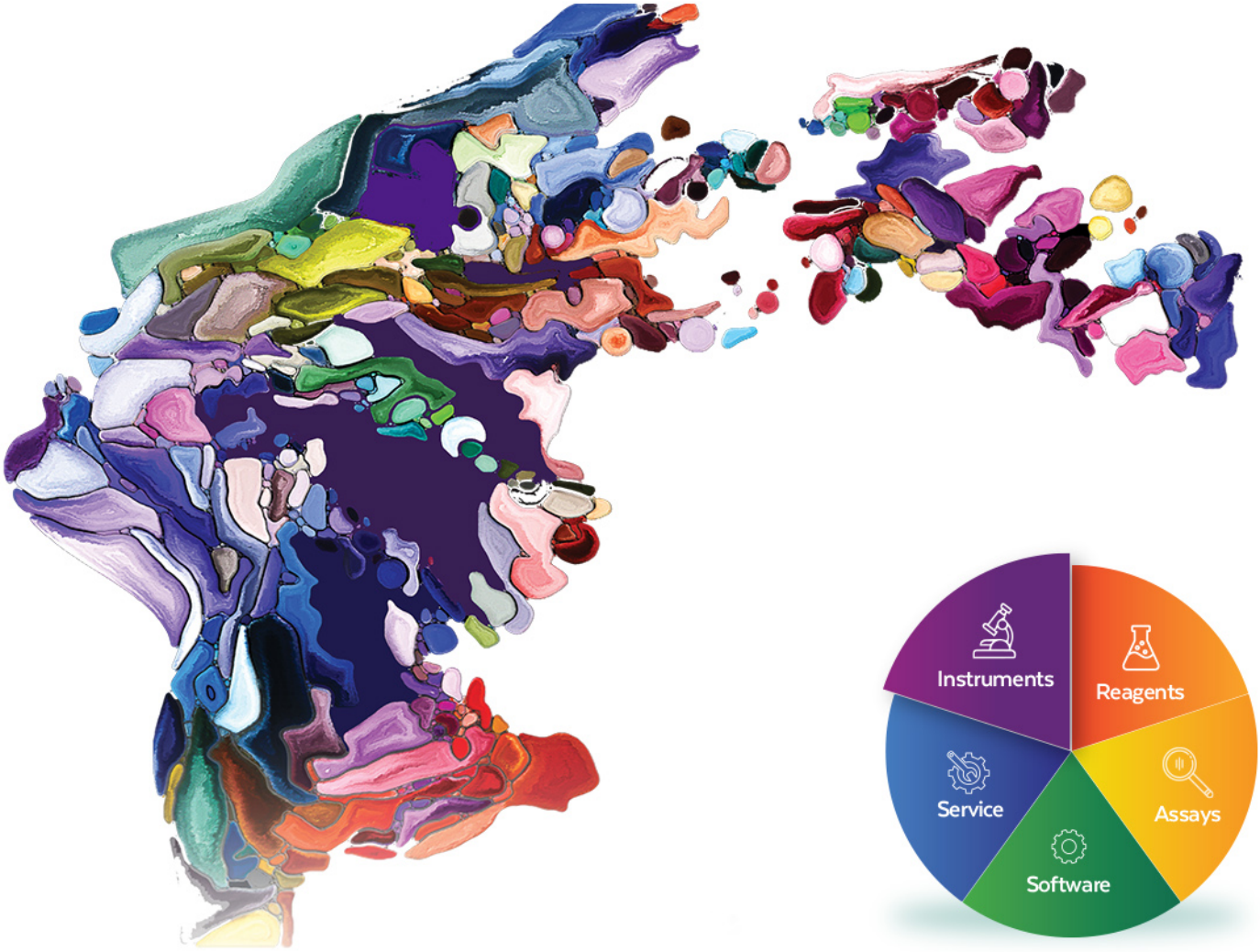

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HIGHLIGHTS

REVIEW

Human dendritic cell subsets: An updated view of their ontogeny and functional specialization

Elodie Segura

Institut Curie, PSL Research University, Paris, France

Human DCs have been divided into several subsets based on their phenotype and ontogeny. Recent high throughput single-cell methods have revealed additional heterogeneity within human DC subsets, and new subpopulations have been proposed. In this review, we provide an updated view of the human DC subsets and of their ontogeny supported by recent clinical studies . We also summarize their main characteristics including their functional specialization.

Keywords: Human · dendritic cell · subsets

Introduction

The heterogeneity of human DC has been described initially based on their surface phenotype [1] and transcriptome [2]. Recently, high-dimensional methods have refined the description of human DC subsets by identifying previously overlooked DC populations. The caveats and challenges of using single-cell transcriptomics for defining novel DC subsets, in particular distinguishing bona fide subsets from transitory cellular states, have already been discussed elsewhere [3]. The consensus nomenclature for DC is based on ontogeny [4], that is, a DC population is considered to represent a distinct subset if it possesses a specific developmental pathway including distinct transcription factors enforcing their lineage commitment and/or identity. Following this nomenclature, human DC can be classified into classical DC (cDC) type 1 (cDC1), cDC type 2 (cDC2), DC3, plasmacytoid DC (pDC), and monocyte-derived DC (mo-DC). As discussed in this review, there is sufficient evidence that these DC populations develop along distinct pathways. A population of AXL^+ $SIGLEC6^+$ DC has also been described, but whether it represents a DC subset remains unclear (discussed in Section "Characteristics of human transitional AXL^+ $SIGLEC6^+$ DC"). Langerhans cells, which are classified as a population of skin macrophages, will not be discussed in this review.

Human DC subset identity is imprinted by their ontogeny, as DC subsets from distinct organs display a common transcriptomic program [5] and shared phenotypic markers (Table 1). In addition, there is a level of tissue imprinting, as specific signatures exist in mucosal tissue DC, for instance, the expression of CD103 for cDC1 or CD1a for cDC2 [5–8]. Of note, there is also significant interindividual variation in the phenotype of cDC2 [7]. Recent single-cell RNA-seq (scRNA-seq) studies have also shown that all human DC subsets express a common activation program upon maturation, both homeostatic and induced by inflammatory stimuli [3].

Ontogeny of human DC subsets

In vitro differentiation models have provided insights into the ontogeny of human DC subsets (Figure 1). pDC and pre-cDC arise from a common dendritic cell progenitor (CDP) downstream of a $IRF8^{high}$ GMDP (granulocyte-monocyte-DC progenitor) [9–11]. A series of studies have shown that pDC in the mouse possess a dual origin, with pre-pDC deriving from CDP or from a lymphoid progenitor [12]. Whether the same holds true for human remains to be determined. Of note, human multipotent lymphoid progenitors have also been shown to give rise to cDC, with a bias toward cDC1 [13]. Pre-cDC display heterogeneity at the transcriptomic level as shown by single-cell RNA-seq, and are precommitted to become cDC1 or cDC2 [14, 15]. $IRF8^{low}$ GMDP gives rise to monocytes and DC3 along separate routes [11].

Correspondence: Dr. Elodie Segura
e-mail: elodie.segura@curie.fr

Correction added on 28 June 2022, after first online publication: The copyright line was changed.

Table 1. Phenotypic markers of human DC subsets

Markers	cDC1	cDC2	pDC	DC3	Mo-DC	CD14$^+$ monocyte
CADM1	+	−	−	−	−	−
CD11c	+	++	−	++	++	++
CD123	−	−	+	−	−	−
CD14	−	−	−	Low to +	+	+
CD141	++	+	−	+	+	−
CD163	−	−	−	+	−	−
CD172a	−	+	−	?	+	+
CD1a	−	Tissue-dependent	−	−	+	−
CD1c	−	+	−	+	+	−
CD226	+	−	−	−	+	−
CD303	−	−	+	−	−	−
CD304	−	−	+	−	−	−
CD5	−	Low to +	−	−	?	−
CD64	−	Tissue-dependent	−	?	+	+
CD88	−	−	−	−	+	++
Clec10A	−	+	−	+	+	−
Clec9A	+	−	−	−	−	−
FcεRI	−	+	−	+	+	−
S100A8/A9	−	−	−	+	+	+
XCR1	+	−	−	−	−	−

Monocytes are included for comparison. Markers are based on selected references [1, 8, 11, 16, 30, 35, 62, 73, 96–99].

Finally, monocytes differentiate into macrophages or mo-DC via two distinct developmental pathways [16].

Studies of primary immunodeficiencies have confirmed the essential role of IRF8 for human DC development in vivo. Patients bearing a dominant negative *IRF8* mutation (resulting in reduced activity) have severely reduced numbers of pDC, cDC1, and cDC2 [17–20], but maintain DC3 numbers [11]. By contrast, patients with a total loss-of-function *IRF8* mutation lack monocyte and DC development entirely [11].

Other transcription factors involved in pDC development include SpiB and E2-2/Tcf4 as shown in in vitro models [21, 22]. Patients with a deficiency in *IKZF1* (encoding Ikaros) have reduced circulating pDC, showing a role for Ikaros in pDC development in vivo [23]. By contrast, patients with a loss-of-function mutation or deletion of *E2-2* have normal numbers of pDC but their phenotype and function are altered, suggesting a role for E2-2/Tcf4 in a late stage of pDC differentiation in vivo [24].

Activation of the Notch pathway inhibits pDC development but is critical for cDC1 differentiation in in vitro culture systems [25–27].

Finally, mo-DC differentiation is dependent on IRF4, Blimp-1, aryl hydrocarbon receptor and NCOR2, as evidenced in in vitro models [16, 28].

Characteristics of human cDC1

cDC1 are found in peripheral tissues and in lymphoid organs. Analysis of mucosal tissues and associated draining LNs has suggested that mucosal cDC1 have lower migratory ability than cDC2 [6]. In lymphoid organs, cDC1 are dispersed in the T-cell areas [6, 29, 30].

Blood, lymphoid organ, and lung cDC1 have been shown ex vivo to stimulate naïve CD4 T-cell polarization into both Th1 and Th2 cells [29–32].

Blood, skin, and lymphoid organ cDC1 are efficient cross-presenting cells, with a superior ability for the cross-presentation of necrotic cell-associated material [8, 30, 31, 33–37]. In ex vivo assays, they also promote the differentiation of cytotoxic CD8 T cells [38, 39].

In terms of cytokine secretion, cDC1 are specialized for the production of type III IFN [38, 40, 41].

Characteristics of human cDC2

cDC2 are found in peripheral tissues and in lymphoid organs, where they are enriched at the border of T–B-cell zones [6, 29]. A recent scRNA-seq study has reported two populations of cDC2 (Clec10A$^+$ and Clec10A$^-$) present in the human spleen, but not in the blood [42]. The significance of this finding is unclear, as these populations have not yet been observed by others. Whether Clec10A$^+$ and Clec10A$^-$ cDC2 constitute distinct subsets or different cellular states remains unclear. In addition, their phenotype may be imprinted by a particular tissue microenvironment and their presence in other organs and tissues has to be confirmed.

Similar to cDC1, blood, lymphoid organ, skin, and lung cDC2 can induce ex-vivo polarization of naïve CD4 T cells into Th1 and Th2 cells [29–32, 43]. Blood and lung cDC2 have a superior ability for the induction of Th17 responses, which is likely

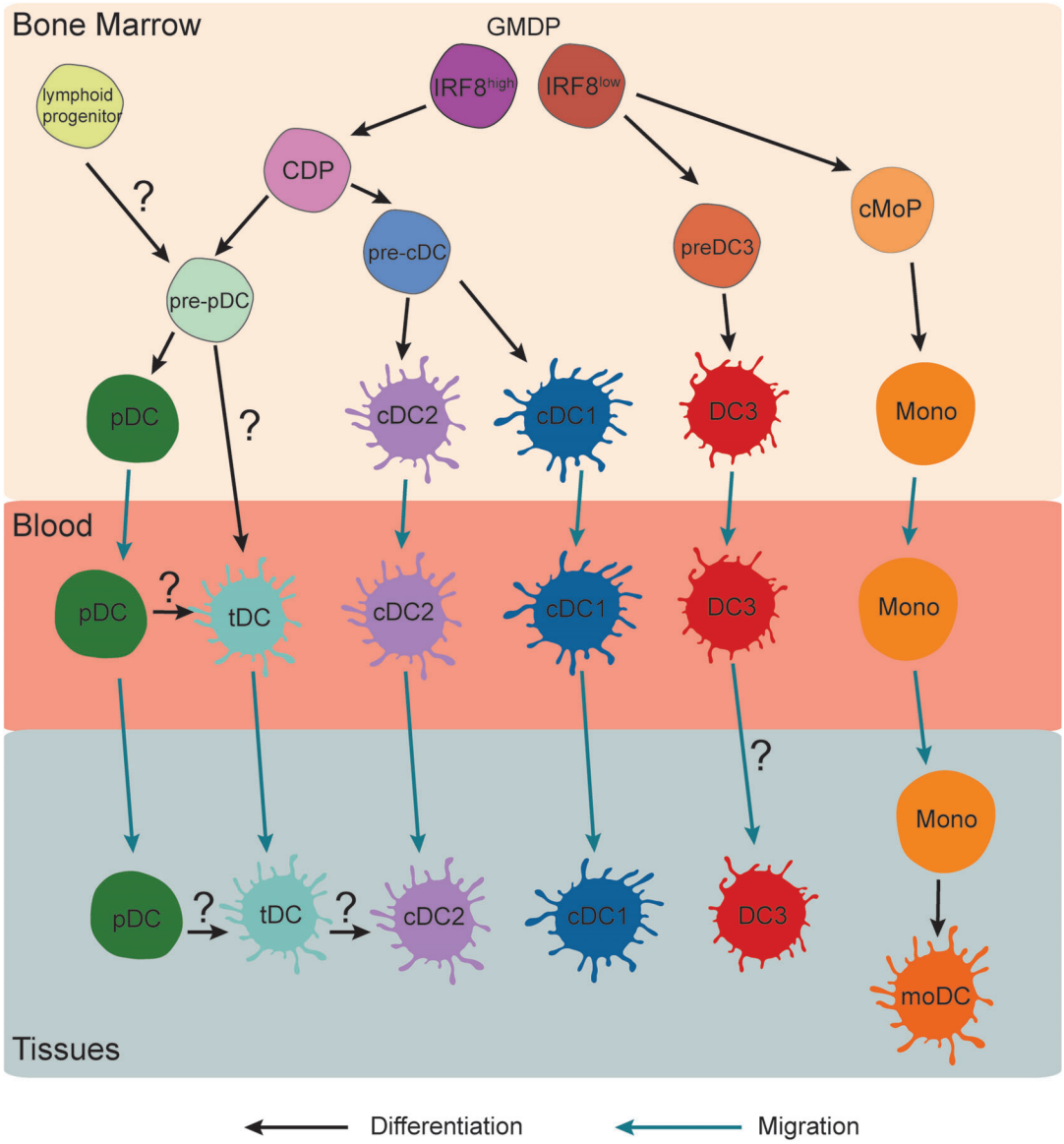

Figure 1. Ontogeny of human DC subsets. DC precursors originate from the bone marrow. pDC, cDC1, cDC2, and DC3 develop from precursors distinct from the other DC lineages. moDC are differentiated from monocytes in peripheral tissues. The developmental pathway of tDC remains to be better characterized. Cell differentiation is indicated in black and cell migration in blue. Questions marks indicate aspects that remain unclear. CDP, common DC progenitor; cMoP, common monocyte precursor; GMDP, granulocyte-monocyte and DC progenitor, mono, monocyte; moDC, monocyte-derived DC; tDC, transitional AXL$^+$ SIGLEC6$^+$ DC.

due to their ability to secrete IL-23 [44, 45]. Blood, lymphoid organ, lung, and skin cDC2 are also the most potent inducers of T-follicular helper (Tfh) cells [29, 46, 47], due to their higher expression of Activin A and OX40-ligand [29, 47]. Consistent with their role in Tfh polarization, lung cDC2 are recruited to tertiary lymphoid organs [47].

In the blood and lymphoid organs, cDC2 are as efficient as cDC1 for the cross-presentation of soluble protein antigens ex vivo [30, 33, 34, 37]. In addition, they can stimulate the differentiation of cytotoxic CD8 T cells [38, 39].

Regarding cytokine secretion, in addition to IL-23 and activin A, cDC2 are the most efficient for the production of IL-12p70 [29, 33, 38].

Finally, intestinal cDC2 are superior to cDC1 for the induction of CD4 Treg, due to their higher expression of integrin αvβ8 which is essential for generating bioavailable TGF-β [48].

Characteristics of human pDC

In the steady state, pDC are present in lymphoid organs but not in peripheral tissues.

The most characteristic feature of pDC is their specialization for the production of type I IFN upon activation [49].

Blood and lymphoid organ pDC are less efficient than cDC for the stimulation of naïve CD4 T cells in the steady state [29].

However, they can become potent stimulators of CD4 T cells after ex-vivo activation, and are able to induce Th1 polarization [49]. It was reported that, upon ex-vivo activation, only a subpopulation of pDC would become APCs, while others would be specialized for the secretion of type I IFN [50]. The physiological relevance of this observation remains unclear. Of note, pDC recognize virus-infected cells via cell-cell contact [51–53], which triggers long-lasting IFN responses without the emergence of an antigen-presenting population [51].

In the blood and lymphoid organs, pDC possess the ability to cross-present soluble, cell-associated or viral antigens in ex-vivo assays [34, 54–58]. However, they are poor stimulators of cytotoxic CD8 T-cell differentiation [39].

pDC are also able to induce CD4 Treg via their high expression of ICOS-ligand [59] or of IDO, an enzyme that catabolizes tryptophan degradation [60].

Characteristics of human DC3

DC3 were initially identified in the blood by scRNA-seq analysis [61]. They express a mixed cDC2-monocyte transcriptomic and phenotypic profile (Table 1). They are best characterized by their coexpression of CD1c and CD163 [11, 62]. They have also been evidenced in the BM [11] and a population with characteristics of DC3 has been observed in oropharyngeal carcinomas [63] and in psoriatic skin [64], but the presence of DC3 in lymphoid organs and peripheral tissues remains to be better characterized. Of note, the term "DC3" has been used to refer to a DC population identified in multiple tumor samples, which should not be mistaken for DC3, as they actually correspond to mature DC [65].

Circulating DC3 are increased in the blood of systemic lupus erythematosus patients and of melanoma patients [62, 66]. DC3 are also specifically increased in the blood of severe COVID-19 patients [67, 68]. Their potential role in the physiopathology of these diseases is unclear.

Blood DC3 are efficient for the stimulation of naïve CD4 T cells ex vivo [61, 62, 69]. DC3 have been reported to preferentially induce Th17 [62] or Th1 [69] polarization, depending on the study.

DC3 can also stimulate the proliferation of naïve CD8 T cells and their expression of maturation markers [69], but whether they can actually cross-present antigens remains to be determined. It has also been proposed that DC3 have a superior ability to induce tissue-resident memory T cells, as DC3 stimulate the expression on CD8 T cells of tissue-homing molecule CD103 [69], and highly express upon type I IFN exposure the costimulatory molecule GITRL [70], which is important for the formation of tissue-resident memory T cells.

Regarding cytokine production, DC3 are able to secrete IL-12p70 and IL-23, similar to cDC2, as well as large amounts of IL-1β, similar to monocytes [11, 69].

Characteristics of human mo-DC

mo-DC share numerous phenotypic markers with monocyte-derived macrophages, and it can be difficult to distinguish the two cell types from one another [71]. A key feature of mo-DC is their dendritic morphology, similar to that of classical DC [72–74], whereas macrophages show a large cytoplasm containing numerous phagocytic vacuoles. Another typical characteristic of mo-DC compared to macrophages is their superior ability to stimulate naïve T-cell activation [39, 73], but this is not always possible to assess due to the challenges associated with cell isolation from human clinical samples. mo-DC also express DC-related transcriptomic signatures [39, 74–76], including transcription factors related to their molecular ontogeny such as IRF4 [16].

mo-DC have been described in clinical samples both in steady state and inflammatory context. mo-DC are present in steady-state peritoneum [72], nondiseased intestine [75, 76], and lungs [77]. A population of $CD14^+$ DC in the steady-state skin is also believed to be monocyte-derived [78, 79]. "Inflammatory" mo-DC are also found in skin from atopic dermatitis and psoriasis patients [80, 81], pleural effusions from tuberculosis patients [82], peritoneal ascites from cancer patients [73], synovial fluid from rheumatoid arthritis patients [73], and intestinal lamina propria of Crohn's disease patients [83]. Finally, cells with phenotypic features of mo-DC have been observed in breast [74], colorectal [84], lung [84–86] cancers, and melanoma-draining LNs [87].

mo-DC from clinical samples efficiently stimulate naïve CD4 T-cell proliferation ex vivo and preferentially induce Th17 cells [73, 82] or Th1 cells [76, 81] depending on the context. mo-DC from skin, synovial fluid, and peritoneal ascites have also been reported to efficiently induce Tfh polarization [29, 30, 43].

Peritoneal mo-DC can cross-present soluble and particulate antigens [39, 72], but use a nonconventional intracellular pathway dependent on lysosomal proteases [39]. mo-DC are also efficient for inducing the differentiation of effector cytotoxic CD8 T cells [39].

Similar to cDC2, mo-DC have been shown to be specialized for the secretion of IL-23 [73, 82] and IL-12p70 [39].

Characteristics of human transitional AXL^+ $SIGLEC6^+$ DC

AXL^+ $SIGLEC6^+$ DC were identified in the blood by scRNA-seq analysis as a subpopulation of $CD123^+$ DC [15, 61]. They have also been evidenced in lymphoid organs but not in steady-state peripheral tissues [7], and are recruited to inflamed skin and lungs [88, 89].

AXL^+ $SIGLEC6^+$ DC display a mixed pDC-cDC transcriptomic and phenotypic profile, however, they are closer to cDC2 functionally. They are efficient for stimulating CD4 T cells ex vivo, and do not secrete type I IFN [7, 15, 51, 61, 90, 91].

Whether AXL^+ $SIGLEC6^+$ DC represent a *bona fide* DC subset or an intermediate population remains to be confirmed

Table 2. Functional properties of mouse and human DC subsets

Function	cDC1		cDC2		pDC		DC3	Mo-DC	
Cross-presentation	Yes	Yes	No	Yes	No	Yes	?	Yes	Yes
Presentation on MHC II	Yes	Yes	Yes	Yes	Limited	Yes	Yes	Yes	Yes
Induction of cytotoxic CD8 T cells	Yes	Yes	No	Yes	No	Limited	?	Yes	Yes
Induction of Th1 cells	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Yes
Induction of Th2 cells	No	Yes	Yes	Yes	No	No	No	?	?
Induction of Th17 cells	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Induction of Tfh cells	No	No	Yes	Yes	No	No	?	?	Yes
Induction of Treg cells	Yes	No	No	Yes	Yes	Yes	?	?	?
Secretion of IL12p70	Yes	Limited	No	Yes	No	No	Yes	Yes	Yes
Secretion of IL23	No	No	Yes	Yes	No	No	Yes	Yes	Yes
Secretion of type I interferon	No	No	No	No	Yes	Yes	No	No	No
Secretion of type III interferon	Yes	Yes	No	No	Yes	Yes	?	No	No

The main immune functions of DC subsets are summarized, for humans and mice DC for comparison. Mouse DC characteristics are in blue, human DC in orange. For mouse DC functions, see details in recent reviews [12, 93, 94]. Question marks indicate that this function has not been reported yet in the literature. Tfh, T follicular helper, Treg, T regulatory.

(Figure 1). Because they can differentiate into cDC2 in culture systems [15, 61, 92], they have been proposed to be DC precursors or a "transitional" population between pDC and cDC2. Their molecular ontogeny remains unclear and might be shared with pDC. AXL$^+$ SIGLEC6$^+$ DC are decreased in the blood of patients with a mutation in *TCF4* [15], suggesting a role for E2-2/TCF4 in their differentiation. AXL$^+$ SIGLEC6$^+$ DC also highly express the transcription factors BCL11A, RUNX2, and SPIB, which are involved in pDC development [91].

Functional specialization of DC subsets

Numerous studies using genetic mouse models have identified specific functions for murine DC subsets and contributed to the concept of functional specializations of DC subsets and their "division of labor" [12, 93, 94]. While DC subsets are conserved between mice and humans [4], their functional properties are not always similar (Table 2). In particular, the ability to cross-present antigens seems to be less restricted in human DC compared to murine DC subsets. However, DC subsets display distinct abilities for antigen uptake, with pDC being inefficient for engulfing large particles and cDC1 being superior for capturing necrotic cells, leading to some specialization in the type of antigen being actually cross-presented in vivo. Another important aspect is their in-situ localization. While different subsets may display similar abilities ex vivo, they may actually play complementary roles in an in-vivo immune response due to their distinct localization or migratory capacity. For instance, monocytes are massively recruited during inflammation, and mo-DC will outnumber other DC populations in the inflamed tissue. With their large array of functional properties (Table 2), mo-DC could efficiently restimulate effector T cells which have been primed by cDC in lymphoid organs, or resident memory T cells being reactivated directly in the tissue.

In addition, when murine and human DC counterparts exert the same function, the precise molecular mechanisms involved can be different. This is the case for Tfh induction by cDC2, which relies on the production by DC of IL12p70 and Activin A in humans, but not in mice [29, 95]. Caution should, therefore, be exercised when extrapolating results from mice models to the human situation, and functional properties, including key molecular aspects, should be confirmed using human DC isolated from relevant tissues.

Conclusions and perspectives

Recent scRNA-seq studies have unraveled underappreciated heterogeneity within historical DC subsets. Based on their distinct ontogeny, human DC can now be divided into cDC1, cDC2, DC3, pDC, and mo-DC. Determining whether Clec10A$^+$ and Clec10A$^-$ cDC2 and transitional AXL$^+$ SIGLEC6$^+$ DC represent additional

DC subsets, cell states, or progenitors requires further investigation. A better characterization of the functional properties of DC3 and AXL$^+$ SIGLEC6$^+$ DC is also needed to understand their potential specialization compared to cDC2. Refined sets of markers should be used in future studies to distinguish and accurately identify human DC subsets, which will be essential for addressing their respective contributions to health and diseases.

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Author Contribution: ES wrote the manuscript.

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Abbreviations: **cDC**: classical DC · **CDP**: common dendritic cell progenitor · **mo-DC**: monocyte-derived DC · **pDC**: plasmacytoid DC · **scRNA-seq**: single-cell RNA-seq · **Tfh**: T-follicular helper

Full correspondence: : Elodie Segura, Institut Curie, PSL Research University, INSERM, U932, 26 rue d'Ulm, 75005 Paris, France.
Email: elodie.segura@curie.fr

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